

Chapter 19

THE HUMAN VOLUNTEER IN MILITARY BIOMEDICAL RESEARCH

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INTRODUCTION

HISTORICAL BACKGROUND OF MILITARY HUMAN SUBJECTS RESEARCH

- Experiments With Mustard Gas
- Experiments With Radiation
- Experimental Administration of Lysergic Acid Diethylamide
- An Army Research Program Develops

ETHICAL GUIDELINES GOVERNING HUMAN SUBJECTS RESEARCH

- The Belmont Report*
- The Common Rule
- Assurances

USE OF DATA OBTAINED WITHOUT CONSENT

ETHICAL CONSIDERATIONS FOR EPIDEMIOLOGICAL STUDIES

ETHICAL PRINCIPLES APPLIED TO EPIDEMIOLOGY

- Individual Informed Consent
- Community Informed "Consent"
- Communication of Study Results
- Harms and Wrongs
- Respect for Social Mores
- Confidentiality
- Conflict of Interest

ETHICAL REVIEW PROCEDURES FOR EPIDEMIOLOGICAL STUDIES

- Representation of the Community
- Assuring Scientific Integrity
- Control Groups

MILITARY REGULATIONS PERTAINING TO HUMAN RESEARCH

- Special Features of Military Regulations
- Rules About Using Patient Records in Military Research
- Special Ethical Problems in Military Research

OTHER TOPICS IN MILITARY HUMAN RESEARCH

- Deception in Military Research
- Classified Research
- Special Compensation Programs
- Electronic Data
- An Example of a Military Human Research Program

CONCLUSION

ATTACHMENTS: SEMINAL DOCUMENTS IN BIOMEDICAL RESEARCH

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Army scientists and research volunteers conducting physiological testing in the “Jungle Room” at the US Army Climatic Research Laboratory (CRL), Lawrence, Massachusetts, 1945, one of five paintings by US Army technician 4th grade Moore, an enlisted soldier assigned to the facility. CRL was relocated to Natick, Massachusetts in 1954 and renamed the Environmental Protection Research Division (EPRD). In 1961, elements of the Armored Medical Research Laboratory joined with EPRD to form the US Army Research Institute of Environmental Medicine (USARIEM). For many years, these art works were scattered. Circa 1983, they were reunited, but then in 1997, they were again separated, with three aside for disposal. Through the determined efforts of USARIEM scientists concerned for the preservation of the military historical record and the conservation of the paintings, they were reunited, refurbished, and reframed in time for the celebration of the 40th anniversary of USARIEM, 1 December 2001.

INTRODUCTION

There are extensive regulations and guidelines that govern what can, after appropriate review, be done in biomedical and behavioral research involving human subjects. These policies, though they may prescribe what scientists should or should not do, cannot adequately cover every situation researchers might currently encounter nor can they anticipate every potential situation that will arise in the future. When disregard for basic human rights in experimentation has occurred even in relatively recent times, it brings to the forefront the need to continually examine the practices of previous scientists to endeavor never to make the same mistakes again. Understanding the history of others' mistakes is a first step in learning to do what is right. Understanding change is part of that. What used to be acceptable practices may seem entirely inappropriate from a more current viewpoint, and there will continue to be phenomenal change. For example, in recent years the human genome has been completely deciphered, mammals have been cloned, and patient records will soon be largely electronic. Technology allows personal and medical information to be kept track of in ways unimagined even a decade ago. What new ethical challenges will these developments bring to research on human health and disease?

As the previous chapters in this volume demonstrate, ethics is at best an imprecise science. Is there even a reasonably clear definition of *right* and *wrong* that can be relied upon today? Even the apparently simple task of defining *research* and *ethics* is deceptively complex. Excellent books have been written on these topics recently,¹⁻⁸ yet none can address every important issue. Can there even be agreement on what constitutes "research" and therefore when a person is a research subject? For instance:

- Is the purchase of groceries in the supermarket consent to being a research subject? If a supermarket keeps track of every purchase a person makes, and then uses the information as an inducement for customers to spend even more, is that acceptable? Do such researchers need consent to study consumers in this fashion? Is the collection of data on purchasing habits research?
- Is the use of the internet consent to being a research subject? If a commercial web site keeps track of every visitor, what they download to their own computers, what they look at, and for how long, and then

target individuals with particular browsing habits for special offers, is that acceptable? Do such researchers need consent to study consumers shopping habits, refining their methods until they define optimum patterns to identify those ready to buy particular products?

- Are individuals wronged if their personal information is used without their knowledge even if they suffer no adverse consequences? Does it matter if the results or methodologies developed are published or just used by the corporation for its own financial benefit? Does there need to be a documented or potential harm to an individual for oversight to be required?

Questions applicable to a military setting include:

- Is a military test pilot (similar to Figure 19-1) engaged in research when testing a new aircraft? Is an Airborne soldier (similar to Figure 19-2) who parachutes with a new parachute and is then asked to fill out a questionnaire on his perceptions of the new parachute a research subject? Are service members departing the front gate of their base research subjects if an inconspicuous person stands nearby recording seat belt usage?
- Are service members completing standardized mail opinion surveys on satisfaction with military life research subjects if the only purpose of the survey is to inform Congress how to improve benefits and retention? Does their status change if the survey collects data on housing costs but is made mandatory by the chain of command?

For our purposes, research is a systematic investigation designed to test hypotheses, permit conclusions, and develop or contribute to *generalizable knowledge*. Not all data collection or experimentation is necessarily research; it could be education or therapy. The difference is primarily one of intent or overall purpose. For example, if a physician finds a patient's condition does not respond to a certain drug, the physician may try other drugs to find one that works better. Provided that the drugs being used are clinically approved (ie, not themselves investigational), such "experimentation" would constitute therapy, not research. Yet, if this same phy-



Fig. 19-1. A pilot awaits clearance for takeoff. Test pilots who evaluate new or recently repaired equipment are not considered research subjects. Photograph courtesy of "Best of the Air Force" CD-ROM, First Edition, 1998. Defense Visual Information Center, March Field, California.

sician decides to try these same drugs on a series of patients to see if the results are the same as they were with the original patient, then this activity would most likely be classified as research. Similarly, a noncommissioned officer (NCO) demonstrating how to make anthropometric measurements for the unit weight management program is engaged in teaching rather than research as long as the activities are confined to a particular class or classes. If the NCO were to make anthropometric measures of service members in several units and compare them to see which unit had the greatest physical fitness, then that would be research.

Research is governed by rules. There are, however, two fundamental problems with rules. First, although they may represent society's collective wisdom at the present time, it is unrealistic to ex-



Fig. 19-2. A parachutist exits a plane. Airborne soldiers who were recruited to participate in a randomized controlled trial of an outside-the-boot ankle brace, in hopes that this new equipment may reduce ankle injuries among parachutists, were briefed thoroughly on the purposes of the study by the investigators, who obtained their informed consent. Photograph courtesy of "Best of the Air Force" CD-ROM, First Edition, 1998. Defense Visual Information Center, March Field, California.

pect that any set of rules can cover every possible ethical situation that might be encountered by researchers. Second, rules seldom keep pace with the many rapid changes in technology, as they do not evolve quickly enough to govern the myriad ethical challenges that are continually emerging. In fact, attitudes and beliefs about what is right and wrong change as the environment changes, as knowledge changes, and as advancing technologies allow individuals to confront new issues and study things that they simply did not have tools to study in the past.

Previous chapters have addressed the consequences of inadequate ethical oversight in human

research. Given that apparent breaches of ethics can happen anywhere, and that many have occurred in recent times, it is clear that there must be vigilance in protecting the rights of research volunteers. Unfortunately, some of the most egregious breaches of ethical conduct have occurred since the Nuremberg Code was written. Most of the time, research investigators have interests that parallel those of the volunteers in their study. For example, research cannot be effectively conducted without the cooperation of the volunteer. (It is important to note that we use the term "volunteer" in the strictest sense; those who were subjected to experimentation in Nazi Germany, for instance, would not be classified as volunteers by any reputable researcher.) If a volunteer is harmed, they are not likely to remain available to continue the research for very long.

However, investigators are also subjected to a host of subtle and often not so subtle pressures to complete a research study. These pressures come in many forms, such as the need to follow rigorous scientific procedures, to remain productive (to satisfy one's superiors, attain a promotion, or otherwise advance one's career), to make efficient use of often scarce research funds, and to stay on schedule so as not to miss a window of opportunity. Many other pressures exist; new ones arise regularly. Because these pressures occasionally run counter to the best interest of the volunteers, a high degree of scrutiny and oversight is required before a study is initiated, as well as during its conduct. Ideally, a thorough review of study activities is also conducted after a study is complete so that problems and potential problems can be identified and dealt with appropriately in the future.

Ethical problems in research arise when scientists knowingly or unknowingly allow external factors to take precedence over the rights of the individual test subject, when they forge ahead unaware of risks and possible safeguards, or, more frequently, when they do not truly understand the underlying principles of volunteer rights. For example, scientists may feel justified in risking the well-being of a few subjects if they believe the benefit to society will far outweigh the risks imposed on a few individuals. Unfortunately this reasoning has led to grave ethical and moral violations. Such transgressions can best be avoided by always putting the rights of the volunteers first.

Much also depends on the attitude the researcher has towards the volunteer. Katz, in writing about why study subjects in the Tuskegee Syphilis Study were exploited, manipulated, and deceived, states, "they were treated not as human subjects but as

objects of research."^{9(p4)} Feldshuh, who wrote a play, "Miss Evers' Boys," about the Tuskegee Syphilis Study, explored the relationship between patients and doctors or volunteers and researchers. After interviewing the physicians and subjects involved in the study, he concluded, "really what I found was a growing adversarial relationship, a sense of an 'I-it' relationship rather than an 'I-thou' relationship; a sense of objectification, a sense of thoughtlessness, a lack of identity."^{10(p32)} An "I-thou" relationship recognizes each person's human dignity. It acknowledges the spiritual nature of humans. Establishing an "I-thou" relationship with one's research volunteers will make it less likely that research ethics will be violated.

The previous chapter pointed out how much negative public sentiment there is concerning military research involving human subjects. One may argue that this negative opinion is not always valid and may not always be based on facts. Nonetheless it exists and military researchers should be aware of this. In addition to the ethical principles that govern human subjects research in the civilian sector, military researchers must have a thorough understanding of all the military regulations that pertain to their research. Knowledge of the regulations alone, however, is not enough to prevent ethical violations during the conduct of military research.

How then does one conduct ethical and scientifically valid military research using soldiers, sailors, and airmen as research volunteers? What are the policies and regulations governing military human research? What can be learned from the past? Are there special considerations for doing research using human subjects in a military environment? For example, how might a researcher's higher military rank, educational level, or social status affect the way he treats a young enlisted person who has volunteered for a study? This chapter cannot possibly cover every aspect of the very complex area of research ethics. Instead, we will provide an overview of military and civilian regulations, as they currently exist, concerning biomedical and behavioral research using human subjects, while providing a reasonable measure of historical context and military perspective. The authors' experience is derived primarily from Army medical research, so many of the examples are derived from Army programs. Because all Army regulations stem from a common Department of Defense (DoD) source, however, there are few differences in oversight between the various military services and thus there should be no difference in the ethical principles that apply to research conducted by any of the military

services. There are a number of issues unique to the military research environment and we will review several of these. We will also describe a unique Army

research program that employs active duty Army soldiers whose principal duties are to be available to volunteer for human research experiments.

HISTORICAL BACKGROUND OF MILITARY HUMAN SUBJECTS RESEARCH

In 1900, one of the earliest examples of military research using human subjects was conducted by Army Major Walter Reed to determine the methods of transmission of yellow fever. The subjects in Reed's study were volunteers who gave written consent after being informed about the risks of the study. Subjects were warned that death could occur as a result of their participation, but at the same time, they knew that they risked dying of yellow fever simply because they were present in Cuba, where the disease was highly prevalent. Risks were minimized through constant observation and the provision of the best medical care then available. Although Reed was a forerunner of the modern principle of obtaining informed consent, this study could not have been conducted today because current guidelines specify that research should not be conducted if death is a likely outcome.

It is not known how widespread the practice of obtaining voluntary informed consent was in military research prior to the Nuremberg Code. An early Army Regulation, *The Prevention of Communicable Diseases of Man—General* dated 21 April 1925, mandated that experimental research should be conducted only on volunteers. In 1943 the Navy conducted a study using prisoners at San Quentin to test an influenza vaccine. The Navy used consent forms and ensured that prisoners were not coerced to participate in the research.¹¹

On 26 February 1953, Secretary of Defense Charles E. Wilson issued a top-secret memorandum based on the Nuremberg Code. Often referred to as CS:385, the Wilson Memorandum¹² (Exhibit 17-3, in Chapter 17, *The Cold War and Beyond: Deceptive and Covert American Medical Experimentation*, provides the text of the memorandum) was not declassified until 1975. It applied only to human research in the fields of atomic, biological, and/or chemical warfare.¹¹ In 1954 the Army Surgeon General's office issued an unclassified memorandum specifying protections of human subjects in research, based on the Nuremberg Code; this memorandum applied to all human research, not only atomic, biological, or chemical testing.¹¹ Even though this memorandum applied only to the Army, the Navy and the Air Force had instituted their own regulations governing such research in 1951 and 1952.¹¹ The continuing history of military human

research contains examples of research that was conducted ethically and appropriately, as well as instances in which transgressions against human subjects occurred. Examples of unethical military human research include the mustard gas experiments in the 1940s,^{11,13} the atomic tests in the 1950s,^{11,14,15} and the lysergic acid diethylamide (LSD) experiments in the 1960s.¹¹

Experiments With Mustard Gas

Although the Navy had used consent forms with prisoners at San Quentin in 1943, the Navy did not do the same when it conducted mustard gas experiments among naval personnel in the 1940s. Nor did they adequately inform the subjects of the nature of the experiments. Almost 2,000 Navy personnel were subjected to these tests during World War II and many have suffered long-term health effects such as chronic laryngitis, chronic bronchitis, emphysema, asthma, chronic conjunctivitis, and corneal opacities.¹⁶ These studies were classified and records of participation were destroyed so it was difficult for former test subjects to receive compensation for appropriate medical care. Congress finally approved compensation for these veterans in 1991, nearly 50 years after their exposure to mustard gas.^{13,16}

Experiments With Radiation

The *Final Report of the Advisory Committee on Human Radiation Experiments* (ACHRE),¹¹ published in 1995, documents many violations of these early DoD and service-specific memoranda concerning the ethical conduct of research. Starting in 1946, with the first peacetime nuclear weapons tests in the Bikini Atoll, until 1963, when atmospheric testing was halted by the Limited Test Ban Treaty, numerous radiation studies were conducted using service members and civilians as subjects. A review of these studies shows some common mistakes in conducting research that still occur today, such as underestimating the risks of a study, confusing research with training, using careless or questionable scientific methods, not informing the appropriate service surgeon general of the research, and not being aware of service and DoD policies governing

research. There was also a problem in determining what was human research and what were normal risks of performing military duties.

In 1951 (prior to the 1953 Wilson memorandum), Dr. Richard Meiling, chair of the Secretary of Defense's top medical advisory group, advocated that soldiers be involved with atomic bomb tests so they might overcome fear of radiation.¹¹ He and his colleagues believed that there were no risks in being exposed to radioactive fallout after a nuclear bomb blast and in fact asserted that the soldiers' fear was a greater risk because the soldiers would be unwilling to enter an area where a blast had occurred in order to complete their mission.

On 1 November 1951, the Army conducted an exercise named Desert Rock I, in which more than 600 soldiers occupied positions 7 miles from ground zero. At the outset of the study (approximately 30 days before the blast) the soldiers were assigned to two groups—(1) the experimental group, and (2) a control group that stayed at home base during the blast. Both groups were given lectures and viewed films about the effects of the bomb blast and radiation safety. Both groups were given questionnaires asking how well they understood the information provided. Several weeks after the blast the same questionnaire was given to the experimental group and the control group.¹⁴ The purpose of the questionnaire was to test how successfully they had acquired and retained information about the blast and whether exposure to the blast helped to alleviate their fears of radiation. Blood pressure and heart rate were also monitored for the experimental group a few days before and several days after the blast, using a polygraph.

In 1952 the Army and the Armed Forces Special Weapons Project determined that the results of Desert Rock I were inconclusive due to poor research design. Nine of the 30 questions on the questionnaire were unclear or erroneous and some questions seemed to be purposely misleading.¹¹ The researchers' preconceived notions may have led to the construction of a questionnaire designed to give the researchers the desired results. This experiment demonstrates the failure to apply several ethical principles. The outcome was that the risks of the research were underestimated, the researchers and commanders failed to obtain voluntary informed consent, and the scientific methods were flawed. Because the researchers believed there was no risk involved in exposure to radiation, they took no safety precautions on behalf of the soldiers exposed to radiation. The military commander did not view this as research but as part of routine training, and

so did not obtain informed voluntary consent from the soldiers who were exposed. Desert Rock I and Desert Rock IV (1951 and 1952, respectively) took place before the Wilson Memorandum, but similar Desert Rock exercises took place after the memorandum in 1953, 1955, and 1957.^{11(pp457-461)}

From 1948 through 1956 the Air Force conducted a series of studies of radioactive clouds. In the early tests, drones, with mice on board, were used to collect radiation samples from the clouds. Manned aircraft later replaced the drones because better samples could be acquired more readily. In 1955 the first manned early cloud penetration study, "Operation Teapot," was conducted minutes after detonation of nuclear test weapons to learn exactly how much radiation penetrates into the human system. Pilots swallowed watertight capsules containing film. Researchers determined that the amount of radiation measured inside the body was the same as that measured outside the body.¹¹

The Atomic Energy Commission had a test-exposure limit of 3.9 roentgens but permitted the four Air Force pilots who flew in "Operation Teapot" to be exposed to 15 roentgens. During "Operation Redwing" in 1956 the authorized test-exposure limit was increased to 25 roentgens. Once again the risks of exposure to radiation were underestimated or minimized. Instead of increasing protection to guard against unknown risks, the investigators did just the opposite and thereby increased the risk.

Some of these studies were conducted under the supervision of Air Force General Ernest A. Pinson, who was also one of the test pilots to fly into the radiation clouds. He later admitted that the scientific knowledge gained by these studies had been previously determined by the drone flights that used mice, and that the data from the human experiments did not add much knowledge to the field. When General Pinson was interviewed in 1995 by the President's Advisory Committee on Human Radiation Experiments he stated that he was unaware of the DoD's 1953 Wilson Memorandum. Had he known about it, "he would have gotten written consent from the people that were involved in this."^{11(p472)} At the time, flying through radiation clouds was seen as a part of the pilot's occupation, not as an experimental activity, even though in this instance data were collected and analyzed for purposes of research.¹⁷

These are just two examples of the many human radiation experiments conducted by the military in the 1950s. The 1953 Wilson Memorandum was not always made known to the investigators conducting these experiments. Sometimes consent was ob-

tained, other times not. Moreover, because many researchers were unaware of the Wilson Memorandum they did not know that their research was subject to review and approval by the appropriate service Secretary. Had these experiments received more scrutiny they may have been modified to reduce the risks or improve the scientific merit.

The mechanisms of the modern-day review committees are structured to ensure that these transgressions do not occur in contemporary research. These mechanisms are guided by sound scientific principle. For instance, if risks are not known they should not be assumed to be minor (it makes more sense to assume the risks could be greater than expected and take precautions to minimize risks); studies may be conducted to evaluate risks without first exposing humans; research must be distinguished from training or other occupational duties; and research subjects, especially when service members, must be given the option not to participate.

Experimental Administration of Lysergic Acid Diethylamide

The Army's experimentation with mind-altering drugs from the early 1950s to the 1970s provides further illustration of the consequences that may ensue when researchers ignore or are unaware of the policies and regulations governing human research. The Army was concerned about other countries using hallucinogenic drugs to incapacitate American troops. Between 1955 and 1967 the Army funded 13 research contracts and conducted numerous in-house studies to determine how lysergic acid diethylamide (LSD) affected a soldier's ability to perform his duties and whether LSD could be effective during interrogations to gain sensitive information.¹⁸ These are certainly valid concerns that were important issues to the military.

Some of these studies were conducted using volunteers, whereas others were conducted using subjects who apparently were not informed that they were part of an experiment. In 1958, for example, an Army soldier named James Stanley volunteered to test the effectiveness of protective clothing and equipment against chemical warfare. He was secretly given LSD without his consent. He did not find out that he had been given LSD until 1975, when the Army sent a follow-up letter to the so-called volunteers who participated in the 1958 LSD studies.¹⁹ His exposure to the LSD most likely was the cause of his hallucinations, memory loss, and periods of incoherence, and may have been the

cause of his violence at home, which contributed to family estrangement.¹⁹ Stanley was clearly not fully informed as to the true nature of the research or the procedures being used in the study. A person or soldier cannot truly be regarded as a voluntary participant in research unless he or she is fully informed that he or she is participating in research activities, and made aware of the risks and benefits this research may entail.

Experiments such as these often become known to the public through lawsuits, presidential investigations, and media coverage. Perhaps less is known about the ethical military research that was conducted, because ethical research does not often attract the attention of the civilian news media.

An Army Research Program Develops

Between 1954 and 1955 a climatic chambers building was constructed in Natick, Massachusetts specifically to conduct climatic research using human volunteers (Figure 19-3). Here soldiers and their equipment could be tested while replicating virtually any climatic condition on earth. In the



Fig 19-3. Constructed in the mid-1950s, and completely renovated in the late 1990s, the climatic chambers in Natick, Massachusetts, can simulate weather conditions as cold as -70°F , with variable relative humidity and precipitation. This arctic chamber and the companion tropic chamber are used to test clothing, equipment, and human physiology under a variety of environmental conditions. Investigators shown here are observing human volunteers in a circa 1958 study in the cold. Photograph: Courtesy of US Army Research Institute of Environmental Medicine, Natick, Massachusetts.

summer of 1955 the building was ready for testing but a pool of soldier research volunteers was needed. Mr. Edwin G. Zelezny (who held the position of Human Research Support Program Coordinator from the establishment of the laboratory until the 1980s) traveled from Natick to the Chemical Corps Medical Laboratories at Fort Detrick in Frederick, Maryland to learn how scientists there recruited soldier research volunteers. In a detailed memorandum for record²⁰ dated 1 July 1955, Mr. Zelezny wrote about this program. From that memorandum, a model was developed for the nascent program to be formed in Natick, Massachusetts. His memorandum states,

To implement the volunteer aspect of the program a Volunteer's Participation Agreement requiring the signature of the individual soldier was prepared by the Chemical Corps legal office.²⁰

The commander of the Chemical Corps Medical Laboratories provided Mr. Zelezny with a copy of the materials from Fort Meade detailing recruitment of military volunteers. Enclosure 2 of this memorandum details the recruiting briefing. There was a 40- to 50-minute briefing to familiarize prospective volunteers on the purpose of the proposed investigations. The briefing was outlined in the enclosure:

Emphasis will be placed on the following:

- a. The completely voluntary nature of the program, stressing individual privilege to withdraw at any time without criticism.
- b. A description of various types of investigations in which volunteers will participate stressing safeguards for the individual.
- c. An orientation on garrison duty at Army Chemical Center, Maryland, while on volunteer status and official recognition on completion of duty.²¹

In a letter dated 10 December 1959, Lieutenant Colonel Carl L. Whitney, the commanding officer of the Quartermaster Research and Engineering Center Laboratories, instructed that the following message be read to all research volunteer candidates²²:

It is recognized that each individual faced with making an important decision, especially while a member of the armed forces will in many cases take a 'what's in it for me' attitude. I'm sure many of you are asking yourself that question right now. That is good: I would like to think that every one of you who volunteer for service as a Quartermaster test subject have considered your decision. I

would like to tell you that every effort will be made to assure that service as a subject under my command will:

- a. Consist of an interesting variety of non-routine assignments of military and scientific importance.
- b. Require a minimum amount of details including KP ["kitchen patrol," ie, working in the mess hall].
- c. Provide a liberal amount of off-duty time.
- d. Insure your right to resign at any time as a test subject.
- e. Provide excellent housing and recreational facilities.
- f. Insure special consideration and concern for your personal welfare and status.

From past experience we can state that the work as a test subject might be expected to be on the difficult side about 20 percent of the time, and considerably less difficult the rest of the time. I honestly believe that those of you who volunteer and pass the selection procedure will consider yourselves as having made the right choice after you have had an opportunity to serve at Natick.

One of the researchers who was there at Natick from the very first of the program and observed its development was Dr. John Kobrick. He began his career as research psychologist for the US Army Quartermaster Research and Development Command in February 1953, before the command was even located in Natick. "Things were simpler then, but we still followed the rules of informed consent. We knew what was right and we just did it."²³ The investigator was credentialed and then it was assumed that he knew what he was doing. Research proposals had to be approved by the investigator's section chief, branch chief, and division chief. Even though there were no formal scientific and human use review boards, at the time, proposals were still reviewed by the chain of command.

To recruit volunteers, Dr. Kobrick and his fellow investigators went to Edwin Zelezny and his pool of volunteers. The investigators briefed these soldiers about their studies and gave them informed consent forms to sign. The procedures are similar to those used today at what is now called the US Army Soldier Systems Biological and Chemical Command (SSBCOM). These procedures are also followed by the US Army Research Institute of Environmental Medicine (USARIEM), which was founded at Natick in 1961. From the beginning, the research scientists at Natick were concerned about the safety and rights of the research volunteers.

There was always a medical officer assigned to the soldier research group whose job was to insure the safety of the soldier-volunteers. The medical officer cleared the soldiers for the studies and monitored them while they were participating.

Unfortunately, during the Vietnam War era there were times when the volunteer status of the members of the test subject platoon at the US Army Quartermaster Research Development Command was compromised. Soldiers were given briefings concerning Natick's mission at their basic training site in Fort Dix, New Jersey. Those who volunteered to come to Natick as test subjects were interviewed and given psychological tests. Those selected to be volunteers were generally very relieved to be assigned to Natick, Massachusetts, rather than being assigned to a unit in Vietnam.

Once these Vietnam-era soldiers arrived at Natick they were given informed consent forms to sign. The various studies were explained to them, and they were assigned to studies. They were also told that if they refused to do two studies in a row they would be sent to Vietnam.²⁴ It is very likely that they

believed that participating in a study, no matter how arduous, was better than being sent to Vietnam. It is clear that the conditions of voluntary consent were violated through the use of coercion.

These Vietnam-era "volunteers" lived together in an open bay room in the chambers building. They spent so much time together on studies that many of them became lifelong friends. In August 1997, 15 of them returned to Natick for a 30-year reunion. Ironically, even though these particular soldiers may have been treated in an unethical manner, many of them still had fond memories of their time as test subjects. None of them could remember anyone refusing to do a study, nor could they remember anyone actually being sent to Vietnam. The studies in which they participated were grueling, but they remember their off-duty time being very pleasant (when they were not testing these soldiers were permitted to do what they wanted). Although they were subjected to unethical research practices they reported that they made the most of their situation. These former test subjects are proud of their assignment at Natick.

ETHICAL GUIDELINES GOVERNING HUMAN SUBJECTS RESEARCH

At the time the military test subject program was developing at the Natick Labs, there were a variety of civilian and military guidelines in place that governed the ethical conduct of research using human subjects. The Nuremberg Code was written in 1949 and adopted by the military in 1953, as the Wilson memorandum.¹² The Army regulation governing human research, AR 70-25, *Use of Volunteers as Subjects of Research*, dates to 26 March 1962. The Declaration of Helsinki was adopted by the World Medical Association in 1964, and has been amended 5 times since then.^{17,25} Most federal regulations governing protection of both military and civilian human subjects were not in place until the 1970s, even though there had been some guidelines in place that were intended to protect the rights of military research volunteers prior to that. Having rules and regulations is a necessary, but insufficient, condition for protecting the service member research volunteer; the rules must be understood and followed in order to be fully effective.

The Belmont Report

The *Belmont Report* is a philosophical statement that is the current foundation of the federal regulations governing the use of human subjects in biomedical and behavioral research in the United States.²⁶ It is named for the Smithsonian Institute's

Belmont Conference Center, where the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research held its initial 4-day session in February 1976. The commission then met monthly for the next 3 years to formulate what is now regarded as the standard for human use research ethics.

Definition of Research

The first section of the *Belmont Report* addresses the importance of distinguishing between research and medical practice. According to the *Belmont Report*, "research" designates an activity designed to test a hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge.²⁶ It goes on to state,

Research and practice may be carried on together when research is designed to evaluate the safety and efficacy of therapy. This need not cause any confusion regarding whether or not the activity requires review; the general rule is that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects.^{26(PartA)}

Distinguishing between research and medical practice is not always easy: a recent example can be drawn from the Persian Gulf War in 1991, when

soldiers were given pyridostigmine bromide (PB) as a prophylactic measure against chemical warfare agents. Soldiers thought to be at risk of exposure to nerve agents were given 90 mg/day of PB for a maximum of 7 days,²⁷ to be followed by intramuscular injections of atropine citrate and pralidoxime chloride by autoinjection if exposure to nerve agents occurred.²⁸ PB had been used at much larger doses for more than 50 years in the treatment of myasthenia gravis, and clinical trials to determine its efficacy in protecting against nerve agents had been done in animals.²⁷ Research in humans that had been conducted to support prophylactic use of PB had demonstrated the absence of serious side effects and effects on tolerance to exercise and stressful environments.²⁸ Even though PB had already been approved as a form of therapy, its prophylactic use against nerve agents was technically at an investigational stage; by rights, the DoD should have obtained informed consent before administering PB and notified soldiers of the investigational nature of this treatment. Due to the military emergency, however, the Food and Drug Administration (FDA) granted a waiver to DoD to allow the administration of PB prophylactically without obtaining informed consent.^{27,29}

This was the first time PB was given as a pre-treatment drug for nerve agent exposure. Due to the nature of the “illness,” (ie, nerve agent exposure), efficacy testing under actual conditions could not be accomplished because exposing individuals to nerve agents in order to test this therapy would itself have been unethical. After the war, it became known that US soldiers were, in fact, exposed to low levels of nerve agents when they destroyed a cache of Iraqi rockets in a weapons depot at Khamisiyah.³⁰ There has been a high level of concern about the health effects that these nerve agents may have had on soldiers in the immediate area, and this situation has, in essence, given rise to a “natural experiment” to study the effect of low concentrations of nerve agent exposure on soldier health. Because none of the soldiers in the area at the time demonstrated any acute effects of exposure to nerve agents, however, none of them took the next step in the treatment protocol (ie, intramuscular injections of atropine citrate and pralidoxime chloride by autoinjection²⁸). Thus there was never an opportunity to study whether prophylactic use of PB is effective in protecting against nerve agents. There have, however, been efforts to document the side effects of prophylactic use of PB among soldiers who took it during the Persian Gulf War. Controversy arose with the publication of an article, “Pyridostigmine Used as a Nerve Agent Pretreat-

ment Under Wartime Conditions,” in the *Journal of the American Medical Association* in August 1991. The article appeared to be a report of a research study, but in fact was a report of an observation of a natural experiment occasioned by administration of PB in the Airborne Corps; there was no research protocol sanctioned by an institutional review board (IRB), and data were collected based on anecdotal observations of the medical officers serving in the field.

Many ethicists believed that the FDA erred in 1990 when it granted a waiver to allow the DoD to administer PB without obtaining informed consent. Whether or not the FDA should have approved the use of PB in this context, the fact that it was administered so widely and that an opportunity arose to study its effects subsequently are great illustrations of both the difficulties of distinguishing between research and medical practice and the inherent problems of using data collected for another purpose. In this case, an approved drug therapy was authorized for a previously untested indication. In authorizing the use of PB for this purpose, the FDA effectively lifted the requirement for informed consent. At the same time, once the drug was administered, a natural experiment was made possible to examine the effects of this treatment in a large number of healthy individuals—an “experiment” that would certainly have been impossible to conduct if consent had been required of all participants. Given that informed consent was not required, is it ethical to collect outcomes data for research purposes? It is beyond the scope of this chapter to attempt to present definitive conclusions on the appropriateness of administering PB under these circumstances, but this example amply demonstrates that these issues are complex and need considerable thought and reflection.

There are many other situations when it may be unclear whether or not research is being conducted, such as in field testing of new military equipment. Sometimes new clothing and equipment are tested and data are collected from soldiers. Other times field evaluations are conducted that are more along the lines of marketing surveys rather than research. When questions arise as to whether a survey might be research, a review by an IRB is warranted (Exhibit 19-1).

Three Ethical Principles

The next section of the *Belmont Report* describes three ethical principles that should guide researchers working with human subjects. They are: (1) respect for persons, (2) beneficence, and (3) justice.

Respect for Persons. The first principle, respect for persons, includes the concept of respect for a person’s autonomy as well as protection for people

EXHIBIT 19-1

RESEARCH VS. PUBLIC HEALTH PRACTICE: WHEN DOES A STUDY REQUIRE IRB REVIEW?

Although guidelines for the ethical review of research are continuously evolving, there is one point upon which there has long been general consensus: that research projects involving human subjects require prior review and approval by an appropriate institutional review board (IRB). The very definition of research, however, involves some ambiguities. The collection or manipulation of data involving human subjects may or may not always be considered research *per se*. Research, as currently defined, occurs when a study is *designed* to contribute to generalizable knowledge.¹⁻⁴ “Nonresearch” activities generally take the form of patient treatment, public health practice, program evaluation, or population surveillance.^{2,5} Public laws provide for oversight of the collection of confidential information without consent by public health authorities and confer special protection of the information from public disclosure. This is generally because many public health efforts involve the routine collection of highly confidential and sensitive personal and medical information essential to protect the public health (eg, mandatory reporting of communicable diseases). In a similar vein, other public health efforts, such as investigation of disease outbreaks, must occur quickly to reduce the spread of the disease and find the source as quickly as possible. Activities undertaken to investigate disease outbreaks involve application of proven public health strategies, not research. Although the activities may involve case-control or cohort study designs, formal statistical analysis of data, and publication of findings and control measures, the purpose of the work is to apply public health practice, not to contribute to generalizable knowledge, as in a research project.^{2,5} While these types of public health activities are generally not designed to contribute to generalizable knowledge, they may often result in publication of findings in the peer-reviewed literature. Thus the distinction between research and nonresearch is anything *but* distinct.

Why do we need ethical review of human research studies in the first place? Ethical review accomplishes several purposes. It provides expert assessment of the safety of any procedures used in a study and it ensures that the autonomy of subjects under study is maintained and that the rights of individuals with diminished autonomy are likewise protected (ie, prisoners, children). It allows an evaluation of risk vs. benefit to ensure that benefits to subjects are maximized while harms are minimized. It helps ensure that any research risks are equitably distributed among populations most likely to benefit from the results. Finally, it ensures that the research design is sound and that those who conduct the research are competent both to conduct the research and to assure the well-being of the research subjects, including obtaining proper informed consent when appropriate.

If we proceed first from the tenet that the common goal of all epidemiologists and public health practitioners is to improve the public’s health using ethically and scientifically sound procedures, while paying particular attention to preserving the rights and protecting the confidentiality of individuals under study, then our debate becomes focused on understanding and improving existing mechanisms to achieve these goals.^{6,7} If we agree that the rights of individuals to protection are paramount, then it is essential to support the ethical principles embodied in the most widely endorsed ethical research guidelines,^{1-4,8,9} robust oversight of public health activities specifically authorized for federal agencies,¹⁰⁻¹² as well as robust oversight of public health practice conducted under public health powers delegated to states by the US Constitution.^{6,13}

Currently, the place to start in determining whether a proposed investigation needs IRB review is to decide whether human subjects are involved and if so, whether the investigation meets the current definition of research. The Code of Federal Regulations, Title 45 Part 46 (45 CFR 46) “The Federal Policy for Protection of Human Subjects (Basic DHHS [Department of Health and Human Services] Policy for Protection of Human Research Subjects),” defines a human subject as a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information. Research is defined as a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge.⁴ If the matter wasn’t confusing enough, some studies, even if research by definition, are nonetheless eligible for exemption from review. Certain specific conditions must be met, however,⁴ and there are varying interpretations of who is authorized to make a determination of exempt status. The Office for Human Research Protections (OHRP) *advises* that the determination as to whether research involving human subjects is exempt should not rest solely with the investigators.¹⁴ Institutions may require review of all research conducted under their auspices, even if the research otherwise appears to qualify for an exemption. Some institutions¹⁵ choose to

(Exhibit 19-1 continues)

Exhibit 19-1 *continued*

provide an additional measure of protection for human subjects by nonetheless reviewing research projects that would be deemed exempt under 45 CFR 46.101(b).

The *Belmont Report*, the 1979 report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research,¹ also defines research and further contrasts it with clinical⁵ practice. Practice refers to interventions (diagnosis, prevention, or treatment) designed solely to enhance the well-being of *specific* individuals, whereas research encompasses activities designed to test hypotheses, permitting conclusions to be drawn, and thereby developing or contributing to generalizable knowledge (expressed or published as theories, principles, or statements of relationships). In this case the benefit potentially extends well beyond the individual as it can be generalized to other individuals or populations. While a practitioner may derive general knowledge of patients in a clinical practice and an epidemiologist may develop knowledge of individuals through observation of a population, in research, the scientific method is used to produce generalizable results suitable for critical evaluation, confirmation, or refutation. The more recent report of the National Bioethics Advisory Commission (NBAC)² also wrestles with definitions of research, human participation, and generalizable knowledge as well as what activities should be subject to federal oversight. The importance of who benefits from an activity is also discussed. In the case of patient care it is unambiguous, as the beneficiary of a treatment is the patient. In the case of research, however, the relationship between individual and investigator is different in that the intent of the activity is to generate knowledge that is of primary benefit to society. This creates a potential conflict of interest between the investigator's desire to pursue knowledge and his or her ethical responsibility to protect the rights and welfare of the research participant.

Deciding whether an activity constitutes research on the basis of whether it contributes to generalizable knowledge is fraught with many difficulties. Such a distinction may have fundamentally little to do with the nature and source of the data or the methods used to accomplish a study. It may also have little to do with the primary status of the agency conducting the study as a public health department, surveillance activity, or research institution. As mentioned, many activities directed by federal, state, and local health departments are essential for carrying out core public health functions, such as assessing public health status or rapidly assessing emerging threats to the public's health. Some public health authorities also undertake research involving human participants that clearly requires IRB review. Public health laws authorize many activities that involve human subjects, including routine collection of personally identifiable medical information without informed consent under mandatory disease reporting. These laws also provide for privacy protections from unauthorized disclosure of this protected information.^{6,13} A dilemma might be thought to arise, however, when a public health practice or surveillance activity, whether routinely or unexpectedly, generates knowledge that, if widely disseminated, might have an effect on the public's health. At some point it will be evident that generalizable knowledge will result. When does such work earn the classification of research, and when is the work or result of the work nonresearch?

To wit, does the publication and dissemination of findings from a public health practice or surveillance project tilt the balance toward a designation of research? The peer-reviewed literature is, virtually by design, the principal medium for dissemination of generalizable medical and scientific discovery (eg, research). Currently, the consensus seems to be that the answer to this question hinges on the original design of the study. If the study is designed at the outset to contribute to generalizable knowledge, it is research. The alternative argument is that if generalizable knowledge is only an unexpected consequence of the work then it may not be research for the purposes of the traditional IRB review requirement. Even if all reports of studies presented for publication in the peer-reviewed literature are not derived from research it may nonetheless be reasonable for an editor to take the posture of considering them research until proven otherwise. Legal and ethical responsibility for assuring protection of participants in human research, however, must rest primarily with the investigators. Ultimately, publication and dissemination of research provides for public disclosure of research methods and design, interpretation of findings, and scrutiny of the integrity of the study and validity of findings.

Authors are typically required, as a condition of publication, to affirm that they have met these standards. At a minimum, all research articles publishing data involving human subjects that are submitted for publication should contain a statement indicating whether they had formal ethical review in accordance with 45 CFR 46 (if in the United States) or the Declaration of Helsinki⁸ (if outside the United States). If the research was deemed exempt under 45 CFR 46, the statement should include who made that determination, and if the study was classified as nonresearch, then a description of the legal basis for that determination should likewise be provided. 45 CFR 46 was last updated in August of 1991, and while it does an adequate job of describing exempt categories of research, it was not intended to address nonresearch and in fact was written with clinical practice in mind, not public health practice.

(Exhibit 19-1 continues)

Exhibit 19-1 *continued*

In 1996, the Council of State and Territorial Epidemiologists (CSTE) issued a position statement calling for OHRP and the Centers for Disease Control (CDC) to address this issue.¹⁶ The CSTE noted that many of the activities conducted by state and territorial health departments are essential in carrying out core public health functions, such as addressing the health status of communities or a state's population through surveillance activities or conduct of outbreak investigations to determine cause and appropriate control measures. They further noted that agencies have a legal mandate to conduct these activities to protect the public health, and commented on the vital role of these activities for the "public health care" of the community. The CSTE's position is that these activities do not constitute research and should not be classified as such. The position statement further indicates that obtaining IRB approval and requiring informed consent of subjects could severely hamper the collection of surveillance data or timely response in outbreak situations. Ethical review of research involving human subjects, as it is carried out in the United States, admittedly can be a time consuming process. The legal mandate for public health departments to perform surveillance arguably could not be fulfilled in a timely and efficient manner if full institutional ethics review was required for all of its activities. Interestingly, the Health Insurance Portability and Accountability Act of 1996 (HIPPA), one of the most stringent sets of rules passed to protect the confidentiality of medical information, includes a "public health carve out"¹⁷ a section intended to ensure unfettered operation of vital public health monitoring efforts.

By clarifying and explicitly identifying the distinctions between public health practice and research, conflict can be avoided and both systems of oversight strengthened. Activities of state and local health agencies are allowed under legal authority derived from the US Constitution and are accountable to the public, which legitimizes these activities.^{6,13} "Defining an activity as public health practice does not absolve the practitioner from attending to issues of patient consent, protection and confidentiality. Rather, it moves the locus for oversight of these activities from the IRB to the appropriate state legislative and administrative codes, rules and regulations governing these activities."¹⁸

Recognizing the absence of any formal guidance on the matter, the CDC issued a white paper "Guidelines for Defining Public Health Research and Public Health Nonresearch" in 1999. This groundbreaking document attempts to differentiate research from nonresearch while providing examples of each in the settings of surveillance, emergency responses, and program evaluation. This document unfortunately is predicated upon acceptance of the current definitions of research, human subjects, generalizable knowledge, and surveillance, any or all of which may be less than satisfactory given the current discussion. The document also does not provide an explicit decision tree that could be followed in making decisions about when and whether to seek or require IRB clearance.

Policy and guidance for the protection of human subjects is not uniform for all types of investigative activities. The authority of OHRP to enforce compliance, for example, derives from a statutory mandate, but is limited to research activities funded by grants and contracts from the federal government. This power stems from a constitutional provision for "conditional spending power" which allows the government to regulate what it pays for. The FDA has separate constitutional authority based on the interstate commerce clause. Of potentially greater concern is that studies funded and conducted using private funds occasionally proceed with no ethical oversight at all.

What is urgently needed is a set of guidelines that clearly differentiates public health practice from research. While both types of activities have existing, strong mechanisms to ensure an adequate and consistent level of ethical oversight, there is considerable ambiguity in the current guidance for differentiating between the two. Consideration should be given to the creation of a new 45 CFR 46 category or categories of exempt activities performed by federal agencies or states under legal authority derived from the US Constitution.¹⁹ This could be done using the three criteria recently established by the US Supreme Court in *Whalen v Roe*⁷ in confirming the authority of states to collect sensitive personally identifiable information without informed consent. The criteria were: (1) the information is reasonably related to a valid public health purpose; (2) disclosure of the information is limited to public health departments; and (3) there are adequate statutory confidentiality provisions in place. The disparate laws and regulations governing public health practice and research need to be updated to eliminate the current ambiguities. Meanwhile, the public health community needs to come together to develop interim guidance with examples that can be used to determine if appropriate oversight of studies involving human participants has occurred.

Sources: (1) National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. Washington, DC: Office of Protection from Research Risks, Department of Health, Education, and Welfare; 1979. (2) *Ethical and Policy Issues in Research Involving Human Participants, Vol. I: Report and Recommendations*. Bethesda, Md: National Bioethics Advisory Commission; 2001 (3)

(Exhibit 19-1 continues)

Exhibit 19-1 continued

Protection of Human Subjects, 45 CFR 46 1991. (4) *Protection of Human Subjects*, 32 CFR 219 1991. (5) Centers for Disease Control and Prevention. *Guidelines for Defining Public Health Research and Public Health Nonresearch [white paper]*. Available at: <http://www.cdc.gov/od/ads/opspoll1.htm>. (6) Gostin LO. *Public Health Law: Power, Duty, Restraint*. Berkeley, Calif: University of California Press, 2000. (7) Supreme Court of the United States. *Whalen v. Roe* 429 US 589. (8) *Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects*. Helsinki, Finland: World Medical Association; 2000. (9) Council for International Organizations of Medical Sciences. *1991 International Guidelines for Ethical Review of Epidemiological Studies*. Geneva, Switzerland; 1991. (10) P.L. 105-85, 111 Stat. 2078 (18 November 1997). (11) *Medical tracking system for members deployed overseas*, 10 USC. 1074f, 2001. (12) Department of Defense. *Implementation and Application of Joint Medical Surveillance for Deployments*. DoD Instruction 6490.3. 1997. (13) Gostin LO. *Public Health Law and Ethics: A Reader*. Berkeley: University of California Press, 2002. (14) Puglisi J. *Engagement of Institutions in Research*. Rockville, Md: Office for Protection from Research Risks. Memorandum, 26 January 1999. Available at: <http://ohrp.osophs.dhhs.gov/humansubjects/assurance/engage.htm>. Accessed: 23 October 2002. (15) US Army Research Institute of Environmental Medicine. *Human Research (USARIEM-M-70-25 M)*. Natick, Mass. 13 November 2001; Date updated: 2 October 2002. (16) Council of State and Territorial Epidemiologists. *Definition of Public Health Research [Position Statement 1996-08]*. Available at: <http://www.cste.org.ps/1996/1996-08.htm>. Accessed: 23 October 2002. (17) *HIPAA Regulations Regarding Public Health Information*, 45 CFR 164.512 2002. (18) Fleming DW, Deputy Director for Science and Public Health. *CDC Efforts to Protect Human Subjects Participants* (memorandum to Centers/Institute/Offices and CDC Partners). Atlanta, Ga: US Public Health Service, Centers for Disease Control and Prevention. 1 June 2001. (19) Levine RJ. *External Review Recommendation: Final Report of the External Review Group to the CDC*. Atlanta, Ga: US Public Health Service, Centers for Disease Control and Prevention; 2000.

Exhibit adapted with permission from Amoroso PJ, Middaugh JP. Research vs. public health practice: When does a study require IRB review? *Prev Med*. 2003(36):250–253.

who may have diminished autonomy. A prospective volunteer should be given all significant information concerning a study's purpose, plan, risks, benefits, time commitment, and measurements in language that he or she can understand. A person must be allowed to make an unpressured, independent decision whether or not to participate in the study. Undue incentives, withholding information concerning risks, the use of deception, or use of jargon are contrary to respect for an individual's autonomy (Exhibit 19-2).

Special considerations are given to vulnerable populations who have diminished autonomy such as mental patients, children, the severely ill, and people with severely limited liberty, such as prisoners. Should soldiers, sailors, and airmen also be considered "vulnerable"? From the beginning of their military indoctrination, they learn to follow the lawful orders of individuals of higher rank. Individuals who typically conduct informed consent briefings for military research tend to be of higher rank or have the title of doctor. There is concern, therefore, that this disparity in rank may inadvertently and unintentionally intimidate those being asked to participate. Therefore, great care must be taken to avoid unintentional coercion and to carefully monitor the informed consent process.

Enlisting in the armed forces does not entail a forfeiture of rights or the loss of one's ability to make sound decisions. If individuals are entrusted to help defend their country, then their ability to make sound decisions as to whether or not they

should participate in military research should be trusted. They have full freedom to make autonomous decisions regarding research participation, even when their full time job is "research volunteer," as is true for some soldiers at the SSB COM in Natick, Massachusetts and elsewhere (Figure 19-4).

Beneficence. The second basic principle outlined in the *Belmont Report* is beneficence. Beneficence is the ethical principle of caring for the welfare of research subjects. It means causing no harm to the subject while at the same time maximizing the benefits of the research and minimizing the risks. Assessing the risks and benefits of the research project is an application of the principle of beneficence. No one should be asked to participate in research that is likely to have little or no benefit. Likewise, no one should be subjected to the possibility of extreme harm even if great benefit from the research is possible, at least not before all the risks are clearly explained and the person has had ample time to fully understand the risks. Is the benefit to society of greater importance than protecting an individual member of that society? Today most ethicists agree that it is imperative to protect the individual from harm even if society as a whole may benefit from the research. A unique question for the military is whether being at war should alter how risks and benefits are viewed. Does the need to protect the individual outweigh achieving potential benefit from research that may be critical to the war effort? Soldiers are placed at greater risk as part of their daily activities than during peacetime because be-

EXHIBIT 19-2

THE ELEMENTS OF INFORMED CONSENT

Federal regulations (45 CFR 46.116) state that investigators must obtain informed consent from all human subject volunteers enrolled in research studies. The regulations make explicit some rules that should be followed in the process of obtaining informed consent. For example, caution must be exercised so that the volunteer is not coerced or given undue incentives to participate, and information about the study is to be communicated to the participant in language that he or she can understand. In addition, several basic principles that should be included in or addressed in the statement of informed consent are presented. Under certain circumstances, which are outlined in the regulations, the institutional review board (IRB) may waive some of these requirements, but, in principle, an informed consent document should address the following points.

1. A statement that the study involves research; an explanation of the purpose of the research; a description of procedures to be followed and identification of which procedures are investigational and which might be provided as standard care to the participant in another setting. Use of research methods such as randomization and placebo controls should be explained.
2. A description of any foreseeable risks or discomforts to the participant, an estimate of their likelihood, and a description of what steps will be taken to prevent or minimize them; as well as acknowledgment of potentially unforeseeable risks.
3. A description of any benefits to the participant or to others that may reasonably be expected from the research, and an estimate of their likelihood.
4. A disclosure of any appropriate alternative procedures or courses of treatment that might be advantageous to the participant.
5. A statement describing to what extent records will be kept confidential, including examples of who may have access to research records.
6. For research involving more than minimal risk, an explanation and description of any compensation and any medical treatments that are available if participants are injured through participation, where further information can be obtained, and whom to contact in the event of research-related injury.
7. An explanation of whom to contact for answers to questions about the research and the research participant's rights (including the name and phone number of the principal investigator).
8. A statement that research is voluntary and that refusal to participate or a decision to withdraw at any time will involve no penalty or loss of benefits to which the participant is otherwise entitled.
9. If the participant is or may become pregnant, a statement that the particular treatment or procedure may involve risks, foreseeable or currently unforeseeable, to the participant, or to the embryo or fetus.
10. A description of circumstances in which the participant's participation may be terminated by the investigator without the participant's consent.
11. Any costs to the participant that may result from participation in the research.
12. The possible consequences of a participant's decision to withdraw from the research and procedures for orderly termination of participation.
13. A statement that the investigator will notify participants of any significant new findings developed during the course of the study that may affect them and influence their willingness to continue participation.
14. The approximate number of participants involved in the study.

Informed consent should be documented in a statement indicating that the participant is making a decision whether or not to participate, and that his/her signature indicates that he/she has decided to participate having read and discussed the information presented.

ing in a war zone inherently increases a person's risk of harm. Should this affect the risk/benefit ratio? These are all difficult ethical questions.

Justice. The third basic principle addressed in the *Belmont Report* is justice. The principle of justice means that the burdens of the research as well as



Fig. 19-4. Investigators in a 1958 study at the Natick Labs attempt to determine how much heat stress is caused by requiring soldiers to wear a protective mask. From its inception, the research program at Natick sought to adhere to ethical guidelines by obtaining informed consent from its volunteer subjects. Photograph: Courtesy of US Army Research Institute of Environmental Medicine, Natick, Massachusetts.

the benefits of the research are shared by the same population. Under the principle of justice, for example, soldier-volunteer testing of the moisture vapor transfer properties of newly designed chemical protective uniforms in the heat is considered appropriate. There are numerous environmental and battlefield conditions that soldiers will be subjected to whereas these conditions rarely apply to civilian workers.

The principle of justice also pertains to issues of gender and race. Historically, test subjects for military research were almost entirely male. This may have been appropriate when the role of women in the services was minimal, but it would clearly be inappropriate now that women comprise a significant and increasing proportion of the active forces. Finding a balance between risk and benefit in human research is often more complicated than it would appear initially. Exclusion of women from physiological testing was fairly common even into the early 1990s because of both assumed and actual confounding factors related to hormonal cycles. In order to achieve sufficient statistical power to compare results between gender-specific subgroups, tests that include women might require a much larger test population. This might result in substantially greater costs, make studies more logistically

complicated (as certain testing may have to be done in a particular phase of the menstrual cycle), and therefore take longer to complete. Caution is also warranted if the research protocol might expose a fetus to potential harms of high or low body temperature, hypoxia, vaccines, drugs, or any of the other physiological or psychological stresses endured by research participants. Investigators must carefully consider whether any of these factors represent sufficient cause to exclude women from research studies.

The racial composition of the volunteer pool is important for similar reasons. Although the differences between racial groups in terms of genetics, physiology, and lifestyle may be less pronounced than the differences between genders, there are nonetheless important differences, and research studies must take this variability among racial or ethnic subgroups into consideration. Guidelines for federally funded research now include provisions designed to prevent the arbitrary exclusion of women and minorities from research. It should be noted that this issue runs beyond the fair distribution of research risks. If some groups are excluded from the research subject pool, then treatments that are uniquely beneficial to them will never be developed. A hypothetical example would be a randomized trial of a promising new treatment for hypertension. If the drug were in fact safe and effective for pregnant women but the study excluded pregnant women, the efficacy of this drug for controlling hypertension in pregnancy might never be known.

How subjects are selected for research is also a direct application of the principle of justice. In the Army and the Navy, the majority of subjects for more-than-minimal-risk research are enlisted personnel. The Air Force has typically used a mix of officer and enlisted personnel for their human research. Is it ethical for enlisted members to bear the burden of research that will benefit all military members? One reason the Army primarily uses enlisted members might be that it is easier for enlisted members to be released from other duties to participate in research. Another reason is that many studies are limited to soldiers aged 18 to 35 in order to reduce risks of high-intensity exercise among an older population. In those instances where a research protocol specifically requires the participation of soldiers over 40, special efforts may be needed to recruit these higher-ranking soldiers. Should rank be a consideration for the military in applying the principle of justice? Although limit-

ing the age of the volunteers has an indirect consequence of precluding participation of certain age or rank subgroups, this may be appropriate when the beneficiaries of the research are in fact from the same subgroup as the volunteers.

The Common Rule

The Common Rule is the federal policy on human experimentation. Before adoption of the Common Rule, each federal agency that conducted re-

EXHIBIT 19-3

DoD POINTS OF CONTACT FOR MULTIPLE PROJECT ASSURANCES

Department of the Army

US Army Health Services Command (USAHSC)
Clinical Investigation Regulatory Office (CIRO)
Health Care Studies and Clinical Investigation Directorate, HSHN - I
Army Medical Department Center and School (AMEDD C&S)
Fort Sam Houston, TX 78234-6100
Phone (210) 221-2511 or 0628; DSN 471-2511 or 0628

US Army Medical Research and Development Command (USAMRDC)
Commander, U.S. Army Medical Research and Development Command
ATTN: Human Use Review and Regulatory Affairs Office (HURRAO), SGRD - HR
Fort Detrick, MD 21702 - 5012
Phone (301) 619-2165; DSN 343-2165

Department of the Navy

Naval Health Sciences Education and Training Command (HSETC)
Commanding Officer, Naval Health Sciences Education and Training Command
ATTN: Code 2MC
Bethesda, MD 20889 - 5022
Phone (301)295-5769; DSN 295-5769

Naval Medical Research and Development Command (NMRDC)
Commanding Officer, Naval Medical Research and Development Command
National Naval Medical Center
Bethesda, MD 20889 - 5606
Phone (301)295-0287 DSN 295-0287

Department of the Air Force

Clinical Investigations and Life Sciences Division
Headquarters Air Force Medical Operations Agency (HQAfMOA/SGPT)
Office of the Air Force Surgeon General
170 Luke Avenue, Suite 400
Bolling AFB, DC 20332 - 5113
Phone (202) 767-5078; DSN 297-5078

Uniformed Services University of the Health Sciences

President, Uniformed Services University of Health Sciences
ATTN: Executive Secretary (for Human Use Review Committee)
Bethesda, MD 20814 - 4799
Phone (301) 295-3303; DSN 295-3303

Office of the Chief of Naval Research (OCNR)

Chief of Naval Research
Ballston Center Tower 1
800 North Quincy Street
Arlington, VA 22217-5660
Phone (703) 696-4767; DSN 224-4767

search using humans had its own guidelines, rules, and regulations governing the research. On 9 November 1978, Congress declared that all 16 federal departments and agencies would adopt the Common Rule as a common core regulation on use of human subjects in research. The Common Rule did not ultimately take effect until 19 August 1991. The Common Rule became part of the specific Code of Federal Regulations for the various departments and agencies. For example, it is Title 45, Code of Federal Regulations (CFR), Part 46 (or 45 CFR 46) for the Department of Health and Human Services' (DHHS) version of the Common Rule. The DoD's codification of the Common Rule can be found in Title 32, Code of Federal Regulations, Part 219 (32 CFR 219), and is essentially the same as 45 CFR part 46 subpart A (the variations pertain to the specific agency identifiers in the Code). This means that the exact same rules that apply to patients or students who are subjects of federally funded research in hospitals and universities also apply to soldiers, sailors, and airmen who are the subjects of military research, although the DoD has added some further restrictions. The Director, Environmental and Life Sciences, Office of the Director, Defense Research and Engineering, Department of Defense, holds the responsibility for ensuring DoD compliance with 32 CFR 219.

Assurances

Every military institute or military agency that is engaged in human research is required to provide to their Surgeon General written assurance that the institute will comply with 32 CFR 219 in its conduct of human research (Exhibit 19-3). These assurances are commonly referred to as Multiple Project Assurances (MPAs), Single Project Assurances (SPAs), or Cooperative Project Assurances (CPAs). An assurance formalizes an institution's commitment to protect human subjects. The requirement to file an assurance is incumbent upon both the "awardee" institution and collaborating "performance site" institutions. According to materials provided by the US Department of Health and Hu-

man Services, under the Common Rule Section 102(f), awardees and their collaborating institutions become "engaged" in human subject research whenever "an investigator (whether professional or student) conducting research obtains (1) Data through intervention or interaction with the individual, or (2) Identifiable private information."³¹

MPAs are granted to agencies that have a research mission that includes use of human subjects; MPAs are typically granted to an institution for a period of 5 years. SPAs are granted to agencies conducting only one human use investigation or by agencies that are new to human research and will be eligible for an MPA after they have been granted a number of SPAs.

The requirement that every military institute or laboratory that conducts human research obtain its own MPA is stated in a memorandum dated 10 June 1993 from the Office of the Secretary of Defense. "Commencing with all proposals initiated on or after 1 June 1993, all DoD Components conducting human subjects research shall institute a DoD assurance of compliance model as required by 32 CFR 219."³²

Research conducted at military installations but funded by the DHHS requires separate assurances. These assurances are filed with the Office for Human Research Protections (OHRP) of the National Institutes of Health (NIH). Until 28 February 2001, these assurances took a parallel form to those described above (eg, SPAs, MPAs). After that date, in order to simplify the process, OHRP began granting Federalwide Assurances (FWAs). Each legally separate institution (ie, awardee institutions and collaborating performance organizations) must obtain its own FWA. These assurances are no longer limited only to DHHS-supported research, to special categories of research, or to individual research projects, but are meant to cover all the research conducted by an institution that receives federal funding. Existing MPAs and CPAs will remain in effect through their current expiration date, or 31 December 2003 (whichever comes first). SPAs will remain in effect through the expiration of their respective grant or contract award and any noncompetitive continuation.

USE OF DATA OBTAINED WITHOUT CONSENT

Sometimes data are found to be useful for other purposes well after the initial time of data collection. For example, suppose a survey collects information on sleeping habits, and it is subsequently learned that fatigue may place individuals at particular risk for certain health outcomes or of making costly mistakes on the job. The volunteers who

completed the survey agreed to provide the information based on a certain research purpose that was articulated to them by the investigators during their informed consent briefing. The investigators would now like to use these data for a new purpose. Do the volunteers need to consent to the use of that data for the new purpose? What if they cannot be

reached to provide consent, or if their sheer numbers makes it impractical to contact them all? There are some general exceptions to the rule of informed consent for the use of existing data. The IRB must consider the content of the original consent form, the objectives of the original data collection effort, any potential to cause harm to the individuals who provided it, and any assurances that may have been made to them at the time they provided the information. For example, if survey respondents are told explicitly that the information provided in this survey will be used only to provide them immediate feedback on their health and will not be divulged to outside individuals for any purposes, it is unlikely an IRB would approve release of the data without consent, however great its value for research purposes.

A different set of circumstances occurs with data that have gained significance due to scientific developments. For instance, the military has been collecting blood samples from service members for

years for the purposes of identifying remains, determining historical exposures to infectious diseases, and for serologic testing for human immunodeficiency virus (HIV) infection. Millions of these samples now exist in deep freeze and are viewed by many researchers as a valuable repository of serologic data for a multitude of studies of infectious disease epidemiology, injury prevention, and other research areas. Although the buffy coat from these specimens (ie, the fraction containing the cells) is discarded, it may nonetheless be possible to recover sufficient DNA (deoxyribonucleic acid) from these samples to allow genetic testing of millions of current and former service members. As technology improves and the methodology to accomplish this becomes available, how will the rights of these individuals be protected? What are the issues? Who decides who gets access? These questions involve the exploration of many ethical issues, both now and in the future as technological advances open more research areas for consideration.

ETHICAL CONSIDERATIONS FOR EPIDEMIOLOGICAL STUDIES

Epidemiology is the study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to the control of health problems. In the past century, epidemiology has been credited with many important advances in the understanding of human health and disease. Some of the knowledge gained through epidemiological studies has been applied to the control of environmental and biological threats to health, such as diseases due to bacterial contamination of drinking water. Epidemiological studies are also primarily responsible for current thinking regarding the health effects of tobacco, the importance of diet and exercise in relation to preventing heart disease, and the use of automobile seat belts to reduce the risk of injury or death during a crash. Although traditional medical research may involve intrusions into a person's body, perhaps to obtain blood samples or tissue biopsies or to administer an investigational new drug, epidemiological research generally involves less invasive methods such as interviews, records reviews, or the statistical analysis of large medical databases. Ethical considerations for epidemiological research are well described in the 1991 International Guidelines for Ethical Review of Epidemiological Studies (see the attachment following the chapter). Because many of the issues are common to all human research, only the key points will be summarized in this section.

Epidemiological research is of two main types:

(1) observational and (2) experimental. Observational studies include (a) cross-sectional studies, (b) case-control studies, and (c) cohort studies, all of which generally involve minimal risk to study subjects. They may involve no intervention other than asking questions, or reviewing reports of medical, laboratory, or radiograph examinations.

A cross-sectional study is commonly done on a random sample of a population. Study subjects may be asked questions or given a survey questionnaire, medically examined, or asked to submit to laboratory tests. The aim is to assess aspects of the health of a population, or to test hypotheses about possible causes of disease or suspected risk factors.

A case-control study compares the past history of exposure to risk among patients who have a specified condition (cases) with the past history of exposure to this risk among persons who resemble the cases in such respects as age and sex, but do not have the specified condition (controls). Differing frequency of past exposure among cases and controls can be statistically analyzed to test hypotheses about causes or risk factors. Case-control studies are advantageous when testing hypotheses about rare conditions, because they can be done with small numbers of cases. They generally do not involve invasion of privacy or violation of confidentiality. If a case-control study requires direct contact between research workers and study subjects, informed consent to participate in the study

is required; if it entails only a review of medical records, informed consent may not be required and indeed may not be feasible.

In a cohort study, also known as a longitudinal or prospective study, individuals with differing exposure levels to putative risk factors are identified and observed over a period, commonly years, and the rates of occurrence of the condition of interest are measured and compared in relation to exposure levels. The number of subjects may be very large, perhaps even in the millions, so it may be impracticable to obtain informed consent from all participants. It is essential to identify precisely every individual studied; this is often achieved by methods of matching that are built into record linkage systems. Once identities have been established to perform data linkage, personal identifying information can be removed, thereby safeguarding privacy and confidentiality. An example of a well-designed study of this type is the Millennium Cohort Study,³³ a 21-year prospective study of the health of US military forces. This study will enroll approximately 140,000 current and former service members, who will give informed consent to their participation, and who will complete periodic surveys asking questions about their health status. Their survey responses may also be linked to existing records that have been or will be collected by the DoD or the Department of Veterans Affairs. Investigators have pioneered methods to allow informed consent to be obtained and data collection to be accomplished using the World Wide Web.

An experiment is a study in which the investigator intentionally alters one or more factors under

controlled conditions to study the effects of doing so. The usual form of epidemiological experiment is the randomized controlled trial, which is done to test a preventive or therapeutic regimen or diagnostic procedure. In order to be regarded as ethical, such experiments involving human subjects should be conducted only if there is genuine uncertainty about the regimen or procedure and this uncertainty can be clarified by the proposed research.

In this form of experiment, subjects are typically assigned at random to receive or not receive the intervention being tested. The experiment compares the outcomes in the two groups. Random allocation of volunteers removes the effects of bias, which would compromise the validity of comparisons between the groups. Informed consent of participants is essential, because it is possible that some harm may befall the subjects.

As in many other fields of biomedical and behavioral research, epidemiology is facing a host of new ethical challenges. Research using very large databases can now capitalize on efficient methods for storage, retrieval, and analysis of information. The combination of powerful computers, advanced statistical techniques, and medical domain knowledge has created exciting new opportunities for epidemiological investigation. Statistical techniques that were until recently too complex even for main-frame computers can now be carried out on the desktop. However, whenever new research opportunities present themselves, careful review is essential to ensure that ethical problems do not arise unexpectedly, and to be sure that the ethical rights of human subjects are protected vigilantly.

ETHICAL PRINCIPLES APPLIED TO EPIDEMIOLOGY

There are a number of ethical principles that must be adhered to in the course of epidemiological research. These include issues pertaining to individual informed consent, community informed "consent," communication of study results, harms and wrongs, social mores, confidentiality, and conflict of interest. Each will be separately addressed.

Individual Informed Consent

Except in certain circumstances, informed consent is usually sought from individuals who will be subjects of epidemiological studies, at the time of their enrollment into the study. An investigator who does not plan to seek informed consent must justify this proposal to his or her IRB and be granted a waiver. An IRB may waive the requirement for

informed consent if it would be impractical to locate subjects whose records are to be examined, or if obtaining informed consent would undermine the purpose of the study. The IRB may grant such a waiver if, for example, prospective subjects would likely change the behavior of interest if they were informed about the purpose of the research, or if they might feel needlessly anxious about why they were subjects or study controls.

For epidemiological studies using existing data that are personally identifiable, the rules for informed consent vary. Optimally, individuals should be informed that data such as occupational records, medical records, or tissue samples are to be used in research, and what steps will be taken to protect their confidentiality. Even though it may seem that use of existing data may cause no additional harm

to the study subjects, the inappropriate disclosure of such personally sensitive information may have an impact on them, and they should optimally have the right to decline to participate in such research. Consent is not required for use of publicly available information, and definitions vary with regard to what information about service members is regarded as public.

Some organizations and government agencies employ epidemiologists who may be permitted by regulation to have access to data without subjects' consent. Access may be ethical on such grounds as minimal risk of harm to individuals, public benefit, and investigators' protection of the confidentiality of the individuals whose data they study. Medical surveillance of injuries and illness for managing medical care needs of service members might be a good example of this.

Community Informed "Consent"

When it is not possible to obtain informed consent from every individual in the subject pool, the agreement of a representative of the community or group may be sought. In designating a representative of a community or group, consideration should be given to the nature, traditions, and political philosophy of the community or group. Representatives may sometimes participate in designing the study and in the assessment of the ethical issues and problems in its design. Large prospective studies of military service members will sometimes enlist members of veteran's service organizations to serve on scientific steering committees in order to represent the interests of the population under study.³³

Communication of Study Results

Part of the benefit that communities, groups, and individuals may reasonably expect from participating in studies is that they will be notified of study findings, both those that pertain to their health individually, and those that stand to improve the health of the larger community to which they belong. Research protocols should include provisions for communicating such information to communities and individuals, giving careful consideration to the literacy levels and comprehension ability of the audience. Participants in epidemiological studies should, however, be advised that it may not always be possible to inform them about findings that pertain to their health as individuals, but that they should not take this to mean that they are free of the disease or condition under study. Although it is not always possible to extract information per-

taining to individuals and their families from pooled data, when findings do indicate that a study subject is in imminent need of health care, he or she should be advised to seek diagnosis and advice from a personal physician.

Harms and Wrongs

Ethical review must always assess the risk that any subjects might suffer stigmatization, prejudice, loss of prestige or self-esteem, or economic consequences as a result of taking part in a study. Investigators must inform IRBs and prospective subjects of perceived risks, and of methods to prevent or mitigate them. Investigators must be able to demonstrate that the benefits outweigh the risks for these individuals. There should be a thorough analysis to determine who would be at risk and who would benefit from the study. It is unethical to expose persons to avoidable risks disproportionate to the expected benefits, or to permit a known risk to remain if it can be avoided or at least minimized. A distinction can be made between causing harm and wronging an individual. In order for an individual to be harmed there must first be a breach of confidentiality. On the other hand, using data on an individual without that person's consent, even when the individual cannot be identified, wrongs the individual by invading his or her privacy or using him or her as a means to an end without permission. There may be times, such as when consent cannot be obtained, in which the public interest in conducting the research outweighs such wrongs to the subject. For such research to be approved, however, confidentiality must be assured, consent must be impractical or impossible, and the research must be of sufficient import.

Epidemiological studies, due to their population focus, have the potential to inadvertently cause harm to groups as well as individuals. These harms might come in the form of economic loss, stigmatization, blame, or withdrawal of services. Investigators who find sensitive information that may put a group at risk of adverse criticism or treatment should be discreet in communicating and explaining their findings. When the location or circumstances of a study are important to understanding the results, the investigators should explain by what means they propose to protect the group from harm or disadvantage. Such means include provisions for confidentiality and the use of language that does not imply moral criticism of subjects' behavior. In the military setting a study looking at risk factors for injury or longevity in service that identify high-risk subgroups might illustrate the point. For example, studies that

demonstrate that women with low physical fitness rarely complete basic training, or that soldiers who live in barracks and drink heavily are at significantly higher risk of assault injury might pose such ethical dilemmas. On the one hand, if the study results are used to design interventions that assist women of low physical fitness to become better prepared for basic training or that help soldiers at risk of assault to reduce alcohol intake, the result may be perceived as positive. On the other hand, if fitness is used as a selection criterion for entrance to the military, or if soldiers in the barracks are subjected to legal interventions to prevent consumption of alcohol, these could be considered harms.

Respect for Social Mores

Disregard of the social mores of the participant's group is usually regarded as harmful. Although cultural values and social mores must be respected, it may be a specific aim of an epidemiological study to stimulate change in certain customs or conventional behavior to encourage adoption of more healthful behavior, for instance, with regard to physical conditioning or risk taking. It is a reasonable assumption that many who join the military are less risk averse than their civilian counterparts. Research that suggests reductions in costly injuries can be achieved by altering the risk-taking behavior of individuals may run counter to the military culture. Although members of communities have a right not to have others impose an uninvited "good" on them, studies expected to result in health benefits are usually considered ethically acceptable and not harmful. It is the role of the IRB to consider a study's potential for beneficial change as well as potential unintended consequences.

Confidentiality

Research may involve collecting and storing data relating to individuals and groups, and such data, if disclosed to third parties, may cause harm or distress. Consequently, investigators should make arrangements for protecting the confidentiality of such data by, for example, omitting information that might lead to the identification of individual subjects, or limiting access to the data, or by other means. It is customary in epidemiology to aggregate results so that individual identities are obscured. Where group confidentiality cannot be maintained or is violated, the investigators should take steps to maintain or restore a group's good name and status. Information obtained about subjects is generally divided into:

- *Unlinked information*, which cannot be linked, associated, or connected with the person to whom it refers. Because specific individuals are not known to the investigator, confidentiality is not at stake and the question of consent rarely arises. Under the Common Rule, this type of research is generally considered exempt.
- *Linked information*, which may be anonymous (the information cannot be linked to a particular study subject except by a code or other means known only to that person, rendering it impossible for the investigator to discover the identity of a particular study subject); non-nominal (the information can be linked to the person by a code, not including personal identification, known to both the study subject and the investigator); and nominal (the information is linked to the person by a personal identifier, usually a name).

Epidemiologists typically discard personal identifying information when consolidating data for purposes of statistical analysis. Personally identifiable data should not be retained in the data sets used for statistical analyses if the analyses could be accomplished without having that information present. When personal identifiers remain in records used for a study, investigators should justify this practice to their IRB and explain how confidentiality will be protected. Even when investigators link different sets of personally identifiable data with the informed consent of the individual subjects, they normally preserve confidentiality by aggregating individual data into tables or diagrams. In government service the obligation to protect confidentiality is frequently reinforced by the practice of swearing employees to secrecy.

Conflict of Interest

It is an ethical rule that investigators should have no undisclosed conflict of interest (such as a financial relationship) with their study collaborators, sponsors, or subjects. Investigators should disclose to the IRB any potential conflict of interest. Conflict may arise if a commercial entity sponsors a study and then wishes to use study results in the promotion of a product or service, or if sponsors attempt to suppress results that run counter to their commercial interest. Investigators and IRBs should be sensitive to even the appearance of impropriety; many committees will reject proposals if there is a risk of conflict of interest.

ETHICAL REVIEW PROCEDURES FOR EPIDEMIOLOGICAL STUDIES

Ethical review procedures for epidemiologic studies focus on three areas: (1) representation of the community, (2) assuring scientific integrity, and (3) control groups. Each will be discussed.

Representation of the Community

The community to be studied should be represented in the ethical review process. This is consistent with respect for the culture, the dignity and self-reliance of the community, and the aim of achieving community members' full understanding of the study. A lack of formal education is not a sufficient reason to disqualify a community member from joining in constructive discussion on issues relating to the study and the application of its findings. Inviting community members to sit on IRBs evaluating research that affects them is one way to accomplish this. Military IRBs often have lay-person representation or service member representatives or both. Another way to accomplish community representation is to invite members of veteran's service organizations to sit on research advisory boards when they exist.

Assuring Scientific Integrity

The primary functions of ethical review are to protect human subjects against risks of harm or wrong, and to facilitate beneficial studies. Scientific review and ethical review cannot be completely independent: a study that is scientifically unsound is unethical in exposing subjects to risk or inconvenience and achieving no benefit in knowledge. Normally, therefore, IRBs review both scientific and ethical issues inherent in the research protocols that come before it. An IRB may refer technical aspects of scientific review to a scientifically qualified person or committee, but must ultimately reach its own decision, based on such qualified advice.

Control Groups

Epidemiological studies that require control (ie, comparison) or placebo (ie, nontreated) groups are governed by the same ethical standards as those that apply to clinical trials. (These are fully detailed in 1991 International Guidelines for Ethical Review of Epidemiological Studies, one of the attachments following the chapter.) Important principles are that^{34(§44)}:

- (i) the control group in a study of a condition that can cause death, disability or serious distress should receive the most appropriate currently established therapy; and
- (ii) if a procedure being tested against controls is demonstrated to be superior, it should be offered promptly to members of the control group.

A study must be terminated immediately if the outcome in one group is clearly superior to that in the other, and then all subjects will be offered the better treatment. Additionally, "stopping rules" should be developed prior to the start of the study so there is a clear plan for determining, as soon as possible, whether one treatment or another is beneficial or harmful. As soon as that determination is made, both the study and control groups should be offered the better treatment.

Random allocation may also cause anxiety if persons become apprehensive or concerned about the reasons for their being chosen or excluded from the experimental regimen or procedure. Additionally, if it becomes apparent which soldiers are in the treatment group, volunteers assigned to the control group may not appreciate their importance to the study. This was a significant issue for a test of an outside-the-boot ankle brace for preventing ankle injuries among parachutists.³⁵ In this study volunteers could not be blinded as to which group they were assigned because the braces were clearly visible and it was necessary to instruct volunteers on proper wear. Some individuals assigned to the control group became less motivated to continue when they were not randomized to the brace group. Because their primary motivation to participate may have been to use the braces and because it was completely within their rights to drop out of the study whenever they choose, it was challenging to maintain the scientific integrity of the study and keep the treatment and control groups balanced. Investigators therefore must carefully communicate to members of the study population some basic concepts about the laws of chance, and reassure them that the process of random allocation is not discriminatory, and that all participants are equally important to the study. Some experiments will include the delivery of an alternate intervention to the control group (a so-called attention placebo) in order to maintain their motivation and interest in remaining in the study. Although such practices may be useful in maintaining balanced intervention and control groups, it is important to ensure that the attention placebo does not influence the variable under study in the control group.

MILITARY REGULATIONS PERTAINING TO HUMAN RESEARCH

Military research that involves use of human subjects is thus subject to the same ethical principles and guidelines that govern use of human subjects in civilian research. The military has additional, unique regulations pertaining to human subjects research.

Special Features of Military Regulations

Two provisions of the law that applies to DoD human research state, "Funds appropriated to the Department of Defense may not be used for research involving a human being as an experimental subject unless (1) the informed consent of the subject is obtained in advance; or (2) in the case of research intended to be beneficial to the subject, the informed consent of the subject or a legal representative of the subject is obtained in advance."³⁶ First enacted in 1972, this law was revised in June 1998.

Human research in a military setting is often more restrictive than in a civilian setting. Even though 32 CFR 219 is the same as subpart A of 45 CFR 46, each service has its own regulations that place additional restrictions on human subjects research. For example, Army regulations forbid testing involving prisoners of war and detainees; most military researchers interpret this as prohibition of testing using prisoners in any setting. Another example is that the services may do research involving children only if there is direct benefit to the child. The child is required to give assent in writing, if capable. In all cases a legally authorized representative must give fully informed voluntary consent in advance of the child's participation in the research.

Before any of the military services may use humans in the testing of equipment, even as "indirect objects" of research in minimal risk studies, the investigator must first get approval from an established IRB. This is true even if the test is as simple as wearing a new pair of laser protective goggles to see if they affect color recognition. Although the Common Rule permits exemption from full IRB review under certain circumstances, the investigator must nonetheless obtain a written letter of exemption from the IRB before proceeding.

Some types of equipment testing are automatically exempt such as test flights of new aircraft flown by test pilots. Evaluations of public behavior are exempt, as are evaluation of educational techniques. Some questionnaires qualify for exempt sta-

tus, although others do not. If the data collected cannot be traced to an individual and cannot harm a person psychologically, socially, or economically, then the use of the questionnaire is exempt. If the questionnaire can be linked to the person (even if the answers to the questions would be unlikely to cause harm if they became public) then the questionnaire must undergo IRB review along with the procedures for giving the questionnaire and for protecting the subject's privacy. If there is doubt as to whether or not a study protocol is exempt, the principal investigator must seek advice from the IRB chair who has accountability for the responsible institution. In cases where an institution does not have an IRB, consultation with a higher command is necessary. If need be, the office of the surgeon general of the individual service can be consulted directly.

Equipment studies may qualify for an exemption or an expedited review. Many of these would be human factors tests involving moderate exercise to test boots, uniforms, or other types of individual equipment. Expedited review applies only to research, tests, and evaluations that involve minimal risk to subjects. The condition of minimal risk is met only when the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater, in and of themselves, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. In an expedited review, one or more committee members assigned by the chair reviews the research proposal and can approve it. If there are questions as to whether or not research is exempt, eligible for expedited review, or requires full committee review, the chair of the IRB is usually empowered to advise the investigator regarding the appropriate level of review required. If even one reviewer questions the exemption or expedited review then the proposal generally must go to through full IRB review.

Prior to, or concurrently with, human use review, research protocols must also undergo scientific review. Some institutions conduct scientific review separately from consideration of human use review, but the Common Rule states that the IRB is responsible for scientific quality even though they may defer scientific issues to a known authority on a given topic. Army protocols are reviewed by local review boards, which play the same role as IRBs in the private sector. If the research involves more than

minimal risk, the protocol is referred to the US Army Office of The Surgeon General's review board for additional review. Navy and Air Force protocols that are determined by local IRBs to be more than minimal risk are forwarded to a central office where one officer reviews them. An investigator cannot begin a study until all these committees have provided written approval of the research. The local commander can disapprove a study that has been approved by the local IRB, but cannot approve a protocol until it has first been reviewed and approved through the complete and appropriate IRB review process.

The military should also provide extra protections for human subject volunteers because of the Feres Doctrine, which prevents soldiers from suing the government. The original intent of this law was primarily to protect the DoD and military commanders from being sued by service members who were harmed subsequent to carrying out a lawful order, especially during battle. This law also effectively prevents military healthcare professionals from being sued for malpractice. The Feres doctrine has survived numerous legal challenges since its inception.³⁷

DoD regulations state that research subjects should be protected from medical expenses that are the "direct result of participation in a protocol involving more than minimal risk."³⁸(§5.3.4) Army regulations state that "volunteers are authorized all medical care for injury or disease that is a proximate result of their participation in research," and outline for provisions about how such care is to be administered and how the costs are to be managed.³⁹(§3.1.k) The Navy also requires that arrangements be made for the provision of medical care to subjects who may be injured in the course of a protocol involving more than minimal risk, suggesting that this may be accomplished through limiting enrollment to persons who are already DoD healthcare beneficiaries or by administratively granting benefits to research participants who are not already covered as DoD healthcare beneficiaries.⁴⁰ It is noteworthy that none of these regulations make any specific provisions about injuries that participants may incur as a result of participation in protocols that involve no greater than minimal risk, given that such protocols constitute the majority of contemporary behavioral and biomedical research. The Veterans Administration revised their regulations in 1998 to include a blanket statement that the VA is obligated to provide medical treatment to subjects who are injured while participating in any protocol ap-

proved by the VA Research and Development Committee, provided that the injury did not occur as a result of noncompliance with study procedures on the part of the research subject or in research conducted for the VA by a non-VA subcontractor or institution.⁴¹ Civilian universities and hospitals that conduct research with human subject participants are obviously not bound by these regulations, and their policies and practices concerning emergency treatment for research-related injuries are likely to vary widely.

Rules About Using Patient Records in Military Research

Army policy dictates that the confidentiality of patient medical records must be protected to the fullest extent possible.

Patient medical information and medical records will be released only if authorized by law and regulation....Within DA, patient medical information and medical records may be used for diagnosis, treatment, and preventive care of patients. Patient medical information may also be used within DA to monitor the delivery of health care services, to conduct medical research, for medical education, to facilitate hospital accreditation, and for other official purposes....Unless otherwise authorized by law or regulation, no other person or organization will be granted access to patient medical information or medical records....Any person who, without proper authorization, discloses a patient's medical information or medical record may be subject to adverse administrative action or disciplinary proceedings.⁴²(Subchap2-2)

Clerical and administrative personnel, such as secretaries, transcriptionists, and medical specialists, often see private medical information and medical records. This access is authorized and necessary for treatment facilities to properly process and maintain information and records. However, the treatment facility commanders must ensure that all persons with access to medical information or medical records are trained in their obligation to maintain the confidentiality and privacy of medical information and medical records. When medical information is officially requested for a use other than patient care, generally only the minimum amount of information needed to satisfy the request is given.

Concerns about confidentiality of medical records have recently led to the development of procedures for exchanging sensitive medical data while pre-

serving the patient's confidentiality. A recent Government Accounting Office (GAO) report describes several techniques such as signed consent forms, masked data sharing procedures, and secure data centers. Masked data sharing includes a number of possible strategies, such as third-party linkage.⁴³ Useful in multicenter studies, third-party linkage allows researchers to share only those portions of the patient's medical record that are relevant to the research question, and researchers agree to have a third-party intermediary encrypt and link data from the various research centers. Data sets processed in this manner contain only the information needed to conduct the analyses, and are stripped of any personal identifiers, making re-identification much more difficult. Other strategies to preserve data security and reduce the risk of re-identification include list inflation or grouped linkage. Although patients and their medical professionals should be vigilant in protecting the confidentiality of medical information, a variety of evolving technological solutions are available to alleviate these concerns while still allowing important research to go forward.

Army regulations make provisions for the use of patient medical records in research, but place some limitations on their use so as to protect patient confidentiality. "Qualified investigators may have access to Army medical records and biostatistical information for research and study,"^{42(Subchap2-8)} subject to approval of the surgeon general. "Access may be granted to records in MTFs [Medical Treatment Facilities] and DTFs [Dental Treatment Facilities], Army record centers, and the facilities of the General Services Administration. Medical records used for research will not be removed from the MTF or DTF."^{42(Subchap2-8)} The surgeons general of the individual military services must approve access to patient records under their control. Prior to release of medical records information for research purposes, the surgeon general must be provided with certification of the credentials of the investigator, a statement of the purpose of the research, and evidence of IRB approval. In addition, the investigator must agree in writing to following conditions^{42(Subchap2-8)}:

- a. Information taken from Army medical records will be treated according to the ethics of the medical and dental profession.
- b. The identities of people mentioned in the records will not be divulged without their permission, and photographs of a person or of any exterior portion of his or her body will not be released without his or her consent.

- c. The researcher understands that permission to study the records does not imply approval of the project or field of study by The Surgeon General.
- d. All identifying entries about a person will be deleted from abstracts or reproduced copies of the records.
- e. Any published material or lectures on the particular project or study will contain the following statement: "The use of Army medical records in the preparation of this material is acknowledged, but it is not to be construed as implying official Department of the Army approval of the conclusions presented."

Recently, many new regulations have been issued on a national level to protect confidentiality of medical records information. The Health Insurance Portability and Accountability Act of 1996 ()⁴⁴ authorizes the Secretary of Health and Human Services to issue regulations applicable to essentially the entire healthcare system of the United States, including the DoD. It will be incumbent upon the DoD to comply with HIPAA regulations when they become effective. Although HIPAA has a "public health carve out" designed to ensure continued use of medical records information in important public health surveillance initiatives, use of medical records for research purposes may become more difficult under these new medical record privacy regulations. As full implementation of these new rules is still underway, it may take a while before the entire impact of HIPAA on epidemiological research in particular is known.

Special Ethical Problems in Military Research

Military researchers who work with human subjects are ethically bound to observe the same protections that civilian researchers must adhere to. There are, however, some special situations in military biomedical and behavioral research that pose ethical dilemmas that civilian researchers may never face. Researchers must be especially cognizant of the hierarchical nature of the military and be certain that it does not interfere with the process of informed voluntary consent. Military hierarchy also carries the potential for conflict between the IRB and the commander. Although both civilian and military researchers often offer incentives to participants in research trials, special care must be taken to ensure that incentives offered to military service members do not become inappropriate inducements. This section reviews these special quandaries that military researchers face.

Dynamics of Military Rank

The most obvious difference between civilian and military research involving human subjects centers around the dynamics of military rank. Does the difference between a private and a colonel influence the private's behavior toward the colonel? Of course it does. Soldiers of all ranks are taught to follow the lawful orders of their superiors. They are also taught that the key word is "lawful." If an order is unlawful then a soldier need not follow it. It is unlawful for superiors to order juniors to participate as subjects in research. Does rank influence the voluntary nature of informed consent? Even when the senior person does not give a direct order to the junior person, the senior person may still exert undue influence. Research has demonstrated that NCOs and officers can exert significant influence over a soldier's food preferences.^{45(p232)} If rank can influence food preference and acceptance it may also influence whether a soldier will participate in a research study.

The final ACHRE Report recommends that no officers or NCOs from a soldier's chain of command be present during recruitment briefings.¹¹ This recommendation has been codified in DoD Directive 3216.2, at least with respect to research involving greater than minimal risk.^{38(S4.4.4)} This directive recommends that if officers and NCOs are also offered the opportunity to participate in such research protocols, they should be solicited in separate recruitment briefings, so that their presence may not exert an unintended influence to participate over more junior soldiers. This may make volunteer recruiting even more difficult because unit leadership may develop distrust for the recruiting process if they are excluded from the recruitment briefings. Instead of encouraging their soldiers to volunteer, which the NBAC is trying to prevent, the unit leaders may encourage their soldiers not to volunteer, making it much more difficult to conduct vital military research. A better alternative may be to train officers and NCOs on ethical principles of human subjects research so that they are aware of the issues and understand the steps that are being taken to treat research subjects ethically. They can then participate in recruitment efforts and informed consent briefings, lending their support to these militarily important research programs while having confidence that the soldiers under their command will be well protected.

Does this make the junior enlisted soldier vulnerable? If soldiers are not informed about the vol-

untary nature of human research conducted by the DoD, they may not know that pressure to participate is not lawful. However, if enlisted personnel are educated about human use regulations and what their individual rights are, they are more likely to feel empowered to refuse to participate in studies. Soldiers have been trained to think on their own and be able to make decisions concerning themselves and their unit's welfare. Leadership training is even given to new recruits during Basic and Advanced Individual Training by having them assume team leader and squad leader positions.

The investigator must establish a friendly, professional demeanor during the informed consent briefing, explaining scientific and medical terms to volunteers in common language without talking down to the volunteers. The investigator should foster an atmosphere of mutual respect, putting the volunteer at ease, so a partnership can be developed. If this briefing is done properly, junior enlisted service members can feel comfortable enough to pose questions to senior officer investigators. It is required that a witness who is not connected to the research group be present, to ensure fully voluntary and informed consent. Another enhancement to insure the voluntary nature of the process is to have the consent forms given back to the impartial witness (either blank or signed) a day after the informed consent briefing. The witness then contacts the investigator to let him or her know who signed up for the study. All of these measures are intended to create a setting where the volunteer feels free to say no.

Pressure to Participate

Other groups of potentially vulnerable subjects include members of elite units such as the Rangers, SEALs (Sea, Air, and Land forces), or Special Forces, and individuals who work for or with the investigators themselves. In the case of Special Forces personnel, there may be enormous pressure on unit members to participate in a study as part of their unit. Esprit de corps may make it extremely difficult to avoid coercion, especially given that some of these units do not do anything unless the whole unit participates. It would be very difficult for one member of a Special Forces "A" team, for example, to choose not to participate if every one else on the team is participating. The DoD acknowledges the intensity of these dynamics of peer pressure, and stipulates in cases when the recruitment strategy for a particular research protocol hinges upon the

enrollment of a percentage of the unit, an ombudsman must be present during the recruitment briefing, to ensure that the individual voluntary participation of each participant is emphasized.³⁸(§4.4.4) To ensure objectivity, this ombudsman cannot have any connection with the research team or with the unit.

Similar dilemmas arise in some foreign cultures where all decisions are made by the tribal leader or elder. This issue can pose particular challenges for US-based IRBs that attempt to review the ethical conduct of research that will take place in another country with a different culture. Whose rules should apply? Is it presumptuous to automatically impose American morals and standards on the conduct of an autonomous group of potential volunteers in a foreign land? This is a particularly important issue because many civilian research experiments are now “exported” to foreign lands where rules of conduct are more favorable, either allowing research to be conducted that would not be possible in the United States or allowing it to be conducted at much less cost. Although the US military may also conduct research on foreign soil, these studies are subject to the same regulations used in the United States. Enforcement of ethical guidelines in the case of privately funded research may be much more difficult, however. Many corporations have subsidiaries in foreign countries that can fund and conduct studies where the rules may be far less restrictive.

In military research using soldier-volunteers, the investigator has a responsibility to brief the unit commanders on the definition of volunteer as spelled out in the appropriate regulation.³⁹ It is the responsibility of both the commander and the investigator to ensure that soldiers participating in research are truly volunteers. This becomes especially important in the military culture, where junior soldiers are accustomed to receiving orders from the top and then executing all instructions. The notion of a volunteer soldier may at first run counter to this culture. Special care must be taken to ensure that this culture does not impinge upon the process of obtaining voluntary informed consent.

It is recommended that an investigator briefs a larger group of soldiers than is actually needed to do the study. It is possible to order service members to attend a briefing, but not to order them to volunteer. If 10 volunteers are needed, briefing an entire company results in less pressure on any individual volunteer. In this way individual soldiers will not feel as though they must participate, allowing the investigator to recruit enough subjects. This

may also mean that the investigator will get more volunteers than necessary for the study, but developing a fair way to select volunteers for inclusion is easier and more ethical than using soldiers who have volunteered under pressure. Thus, there are many ways, even in a military setting, to guarantee that military subjects are indeed true volunteers.

Vulnerable Participants

Vulnerable individuals presumably need additional protection in research. A designation of vulnerability can, however, be either useful or potentially harmful. Although certain individuals and populations may be more vulnerable as human subject volunteers than others, people whose circumstances render them vulnerable have at times been arbitrarily excluded from research for this reason alone. Certain individuals have been considered more open to harm (eg, children, the mentally retarded), more subject to coercion (eg, prisoners), more “complicated” (eg, women, who may be considered more biologically complicated than men), or more inconvenient (eg, women with small children, who could be viewed as less reliable research participants due to conflicting demands on time). Labeling otherwise competent people “vulnerable” can be both insulting and misleading. It is not their gender or other group designation that exposes them to injury or coercion, but rather their situation that can be exploited by ethically unacceptable research. That is, it is their circumstances, which are situational, that create the vulnerability.⁴⁶

Probably the most vulnerable group of volunteers consists of seriously ill people volunteering for a study that might help improve their prognosis. This group of subjects is not listed as a vulnerable category, perhaps because it is their illness that makes them candidates for such a study. Doctors have a major influence in persuading these patients to participate in research. The Advisory Committee on Human Radiation Experiments conducted a study on why patients volunteer for research, and found that 67% volunteered because they believed they would get better treatment by participating in research and that 7% said they participated because it was their only hope.¹¹ Some patients who were interviewed by the committee said that they trusted their doctors implicitly and would do whatever was recommended. “Oh, I love that man. He has kept me alive and I obey him and I do what he tells me to do.”¹¹(p740) Of the group surveyed, 10% had decided not to participate in the research.¹¹ Of those who did

participate in the research, fewer than 2% reported that they felt pressured to volunteer.¹¹ The argument can be made, however, that these people were a vulnerable population even though they may not have realized it. It also shows the enormous trust placed in the medical profession and is a reminder that doctors should be conscious that their stature in the eyes of their patients may exert undue influence in the process of obtaining informed consent.

Participation of Members of the Research Team

In the military setting, and perhaps also in civilian settings, colleagues, members of the research team, and occasionally even the investigators themselves will volunteer to participate in the research. This has the potential benefit of allowing study personnel to gain firsthand experience of what it feels like to be a research volunteer. Caution is warranted in these circumstances, however, because an individual may be inadvertently or subtly subjected to pressure to volunteer. This risk is especially true if it turns out to be difficult to recruit volunteers, whether for administrative reasons or because of the arduous nature of a particular study. A recent tragic example of this issue occurred in the summer of 2001 at Johns Hopkins University. A 24-year-old healthy woman who was employed in one of the laboratories volunteered as a research participant in an asthma trial but died as a result of complications from the treatment protocol.⁴⁷ This case sparked an intensive investigation and received widespread media attention. One of the criticisms that was leveled at the investigator and the university charged that she may have been subtly and inappropriately pressured by her employer or by her colleagues to participate in the experiment.⁴⁷

Incentives to Participate

Incentives are important variables in this equation of a subject's decision whether or not to participate in a study. Incentives may be tangible or intangible. Tangible incentives for military service members might be monetary such as environmental stress pay or payment for blood draws. Sometimes individuals must travel in order to participate in research; special allowances for per diem given to military volunteers can also represent an inducement to participate in research. Other tangible incentives may be equipment or clothing that an individual may be allowed to keep when a study is over, such as boots, parkas, or other uniform items. Intangible incentives include factors such as the opportunity to avoid less desirable work or as-

signments (such as happened in the Vietnam era) and recovery time or weekend passes that can be used later. It is important to recognize not only that soldiers or patients may belong to a vulnerable category, but also that they might be vulnerable to external pressures or incentives. It is imperative to nullify these pressures in the informed consent process, not only for military volunteers, but also for volunteers in civilian studies.

Research With No Direct Benefit for Test Subject

Some research is conducted in military hospitals where sick soldiers may receive direct benefit by participating in research designed to test what may be an improved treatment for their illness. Other military research involves testing healthy research volunteers who receive no direct benefit from the research (Figure 19-5). Should the military be involved in this type of research? Yes, according to the principle of justice as defined in the *Belmont Report*. The burden for the research should be born by the people benefiting from the research. Most research being conducted by the military is directly applicable to the military's unique mission and will thus benefit soldiers everywhere, even though the individual soldiers involved in the research may not



Fig. 19-5. The climate chambers are an important resource in the development of clothing or protective equipment. This 1990 photo shows a firefighting suit developed by the Navy. Although the soldier who is volunteering to test this suit for the US Navy may not derive any direct benefit from his participation in research, this work will benefit thousands of other soldiers, and is thus permissible under the principle of *justice*. Photograph: Courtesy of US Army Research Institute of Environmental Medicine, Natick, Massachusetts.

derive benefits directly through their participation.

Military service members need to be able to deploy globally with little advance notice. These deployments often involve rapid relocation to areas with extreme heat, cold, or altitude. When civilians subject themselves to these environmental extremes they usually have the opportunity to do so more gradually. Civilian mountain climbers, for example, can spend several days at camps at various altitudes so their bodies can adjust to the lower concentration of oxygen in the atmosphere, thereby minimizing the impact of altitude sickness. Military members may not have this option due to the urgency of the mission. For this reason, USARIEM conducts studies to determine how to prevent heat illness, altitude sickness, and cold injury.

Soldiers must maneuver in hot, dry deserts and in steamy jungles. Military occupations are physically demanding, and there is often the further strain of imminent enemy contact. Soldiers cannot usually opt to rest in the shade when they begin to feel hot. Moreover, during the Persian Gulf War, there was an added danger of chemical warfare. Soldiers were issued chemical protective clothing and protective masks, but this equipment may significantly increase the risk of heat-related illnesses. Very few civilian occupations require this type of exposure to heat. Military research has also led to the development of hydration regimens that have benefited soldiers. For example, large quantities of water were shipped to the Persian Gulf, preventing numerous heat casualties.

The US Army SSB COM also researches measures to enhance the environment for soldiers and develops new clothing, individual equipment, and food for the military. For example, studies are conducted on backpacks to determine the proper center of gravity to minimize muscle strain among soldiers carrying heavy loads for long periods of time. Boots are tested to make sure they will keep feet warm at sub-zero temperatures. Chemical protective clothing is tested on soldiers exercising in the heat to see how long soldiers can operate without suffering heat-related illnesses. It is useful to get feedback during the development of these items from the soldiers that will be using the items, but such research must always adhere to guidelines that protect human subjects.

Because the military may be deployed globally, the armed forces must be prepared to vaccinate its members against diseases that are not found in the United States. Pharmaceutical companies, however, have few financial incentives to develop vaccines for diseases that are uncommon in the United States. The US Army Medical Research Institute for Infec-

tious Diseases (USAMRIID) develops vaccines, drugs, and diagnostic tests to protect military members from disease and biological agents.

The Air Force conducts studies with human subjects to acquire data on responses to various types of stress experienced in acceleration and high-gravity (high-g) forces to protect the crews of high-performance aircraft and other aerospace weapons systems. These data are also used for operational planning. Similarly, the Navy conducts research on the impact of decompression on sailors who are divers or assigned to submarine duty.

At all of these research centers, healthy service members are asked to volunteer for research that does not benefit them, but which is expected to benefit military members facing difficult conditions. These subjects are told that they will receive no direct benefit from participating in the research. All risks are carefully explained to them. They volunteer for many reasons. Most say they are proud to be able to positively affect the health and welfare of soldiers on future battlefields. Some of these service members plan careers in the healthcare industry; participating in research is of special interest to them. Some can pursue college courses during the evenings or weekends when they are not testing. Taking courses while assigned to a research center is easier than if they were assigned to units that may deploy to the field at any time. The service members who volunteer to participate in military research generally report that they like the assignment and have a sense of accomplishment and contribution.

Potential for Disagreement Between the Commander and the IRB

These service members should be well-protected by the local IRB. A great deal of authority was given to IRBs when they were set up in the late 1970s. Even though they are called institutional review boards their purpose is to protect the research volunteer, not the institute, and military IRBs are no exception. The IRB forwards its decisions to the institute commander. According to 32 CFR 219.112, the commander *can* disapprove protocols that the IRB has recommended for approval, however, the commander cannot approve a protocol that the IRB has rejected. This can create tension in a military setting because in most cases the commander bears responsibility for everything and everyone under his command. If an investigator complains to the commander that the IRB is being unnecessarily slow, bureaucratic, or unreasonable in its decision to disapprove his study, the commander cannot

decide to overturn the committee's decision even if the commander agrees with the investigator. Commanders do approve the IRB membership, but regulations require a diverse group to represent a spectrum of viewpoints and expertise. Sometimes the IRB will disagree with investigators and even the institute commander. This is expected, and when it happens, it demonstrates that the IRB is functioning independently. Commanders of research institutes realize that there will be times when disagreements arise. When the IRB is protecting the research volunteer, it is ultimately protecting the institute as well. Additionally, IRB members have the right to file a "minority report" if they disagree with a final IRB decision.

The Perception of Risk vs. Reward

Another unique ethical problem for the military research community is fear of war. Given a choice, many individuals would choose to participate in military research rather than be deployed to a war zone. Arguably, this was the case for most of the soldiers who volunteered to come to Natick Labs during the Vietnam era. One of the best recruiting trips for human research volunteers for the Natick Research Development and Engineering Center occurred at Fort Benning, Georgia in early February 1991. The air war had just started in Iraq, and the audience of newly trained infantrymen knew the ground war would start soon. Many decided to volunteer to go to Natick as human research volunteers.

People's behavior and the choices they make vary according to their values and goals and a plethora of other factors and influences in their environment. This is the way things should be. It is nonetheless important to be sensitive to situations where the forces acting on one side of a decision grow so strong that a person really can only make one choice. Even if every reasonable person would agree with a given decision, there may still be situations where free choice is nonexistent and informed consent is meaningless.

This sort of situation might develop in acquired immunodeficiency syndrome (AIDS) or cancer research when an individual must choose between near certain death or a high-risk, high-side-effect treatment with a low probability of success. Consider the quandary of a father who is the only tis-

sue-compatible kidney donor for his daughter. He knows she will die if he doesn't donate a kidney. Such an example may not relate to consent for research per se, but it does illustrate the difficulty in obtaining true consent when a person is under significant duress. When faced with such a decision an individual may find it nearly impossible to objectively consider the many significant risks of the procedure.

If the good of the many can ever be more important than the needs of the few, these cases may provide the examples. This is why ethical decision making is so complex. One could no sooner argue that a young girl's life is less important than a father's right to free choice than one could argue that the need to stem the spread of the AIDS epidemic is less important than an individual's right to offer himself to further efforts to develop a cure, even if he is unlikely to benefit and may even suffer from participation in the research.

Likewise it may not be the best policy to stop doing human research during times of war to preclude the likelihood that the fear of war influences people's propensity to volunteer, because commanders may need information from the research to help make decisions on deploying their soldiers in the war zone. For example, shortly after US troops deployed to the Persian Gulf for Operation Desert Shield in August 1990, the surgeon of the 18th Corps needed immediate information on the side effects of pyridostigmine bromide (PB) on soldiers operating in the heat. USARIEM quickly mounted a study in the climatic chambers at Natick using soldier research volunteers to expeditiously find the answer to the question asked by the corps surgeon. Side effects among soldiers operating in the heat and taking the recommended dosages of PB were found to be minor, especially when compared to the threat of Iraqi nerve agent use against US troops. With this information the corps surgeon was able to make an informed decision to administer the pretreatment drug for nerve agent. Questions will arise in future conflicts that will need immediate answers, thus military researchers will need to recruit research volunteers even during times of war. Because service members may be more likely to volunteer in times of war, there is a need to be even more careful to be certain that they are fully informed.

OTHER TOPICS IN MILITARY HUMAN RESEARCH

Other issues that confront military researchers include if and when it is appropriate to use deception, challenges that surround special compensation

programs for research subjects, and use of electronic data. This section reviews these issues and describes a unique Army program that recruits and manages

a pool of active duty subject volunteers while implementing existing procedures designed to protect their rights as volunteers.

Deception in Military Research

Under what circumstances, if any, can the military engage in deceptive research? The very thought of any type of deception in military research is chilling. An immediate reaction may be that the military should never engage in any type of deception while conducting human research. However, there are interesting and important research questions in behavioral science that require withholding the true purpose of the study from the volunteers until after the study is completed, even though the volunteers need to be told exactly what will happen during the research. In a previous example, we mentioned a study that examined how an NCO's or officer's opinion of food influenced how much food was eaten by lower ranking soldiers. The soldiers were told that they were being asked to volunteer for a consumption study of new rations. They were told that they would be asked their opinions about the new rations and the leftovers from their meals would be collected to measure how much they consumed. What they were not told was that the NCOs and officers would be making negative comments at one meal, positive comments at another meal, and no comments at a third meal, for the purpose of finding out if rank can influence ration preference. This purpose could not have been achieved if that was told to the soldiers before they participated in the study.

Was this study authorized under 32 CFR 219? Yes, because according to 32 CFR 219.116(d) this study met all the requirements for an IRB to waive all or a portion of informed consent. The requirements are: (a) the research must involve no more than minimal risk; (b) the waiver must not adversely affect the rights of the subjects; (c) the research could not be carried out without the waiver; and (d) after their participation the subjects should be given a detailed description of the true nature of the study and any other pertinent information.⁴⁸

All human research that involves any type of deception must be reviewed by an IRB. Only the IRB has the authority to waive all or a portion of informed consent. These types of studies seem benign because they pose no risk to soldiers. Nonetheless, investigators must submit a full protocol to the IRB if they plan to withhold any information no matter how minor that information may seem to them. A now famous study conducted in the early 1960s⁴⁹ asked volunteers to deliver shocks to a second individual in order to improve the second

individual's ability to answer questions correctly. The second individual wasn't actually receiving any shocks, and the true nature of the experiment was to see how far people would go in following instructions of the investigator even when the second individual "showed" substantial distress from the shocks. Surprisingly, these volunteers followed the instructions of the investigator even when they believed they were causing the second person substantial harm. It is unlikely that such a study would be approved under current ethical research guidelines.

As already stated, Title 10 of the United States Code, Section 980 (10 USC 980) stipulates that DoD can perform research with human subjects only if informed consent is obtained in advance. This may suggest that DoD should not be involved in any type of research where all or a portion of informed consent is waived, and that 10 USC 980 and 32 CFR 219 are in disagreement on this point. Paragraph 32 CFR 219.116 spells out exactly what is included in informed consent.⁴⁸ A simple definition is that informed consent is a person's voluntary agreement, based on adequate knowledge and understanding of relevant information, to participate in research or to undergo a diagnostic, therapeutic, or preventive procedure.⁵⁰ Moreover, no rights can be waived as a part of informed consent. Based on this definition of informed consent and the criteria given in 32 CFR 219.116(d), there may be instances when DoD investigators may ethically be permitted to conduct research involving elements of deception. Interpreting the regulations governing human research, however, can be very difficult. That is the reason military investigators wishing to do research involving deception must submit their proposals to the IRB. It is the responsibility of the IRB to evaluate these issues and make a recommendation to the commander.

Classified Research

The ethical review of classified research poses particular challenges for IRBs. Historically, some of the DoD's worst transgressions in ethical treatment of human subjects have arisen from studies that were kept secret in the interest of national security. Although there may have been legitimate national security interests in doing so, the results were sometimes horrific. The ACHRE report stated that the IRB chair could remove the classified portions of the research protocol prior to IRB review, provided that they did not bear on risk to human subjects.¹¹ If, however, the classified portions of the protocol did bear on subject safety, then the IRB members (including at least one member not affiliated with the agency or institution) must have appropriate

security clearances in order to review the protocol. A protocol's status as classified also raises issues in the assignment of study personnel (eg, medical monitors) and in the briefing of the volunteer recruitment pool. Briefing the volunteers may need to be done using special procedures, and the medical monitors of the study or the volunteers themselves might also require security clearances.

In response to the concerns raised by the ACHRE over past errors in classified research, President Clinton issued a memorandum with proposed revisions to guidelines concerning use of human subjects in classified research.⁵¹ These guidelines are an attempt to balance the interests of national security with the moral and ethical obligations to protect the rights of human subjects who participate in such research. They prohibit waiving the requirement of informed consent and further prohibit the use of expedited review for classified research protocols. Researchers are required to notify subjects that the research is classified and to inform participants of the identity of the sponsoring Federal agency. The regulations specify that permanent records must be kept indefinitely on classified research. The ACHRE had made a recommendation that classified research protocols should be reviewed by an independent panel of nongovernmental experts and citizen representatives to protect the "interests of the public in openness in science and in government."¹¹ The new regulations stopped short of implementing a separate oversight panel, but stated that IRBs for secret projects should include a nongovernmental member with an appropriate security clearance. Changes were also instituted in the approval and appeals process. Under the Common Rule, the IRB may approve a research protocol if a majority of its members approve the project.⁵² The new guidelines concerning classified research state that if a minority of members of the IRB feel a classified research project should not be approved, they are allowed to appeal majority decisions to the head of the sponsoring Federal agency, and then to the Director of the White House Office of Science and Technology Policy. Clinton's memorandum called for amendments to the Common Rule to reflect these changes. The Secretary of Defense endorsed the proposed policy changes in December 1999, but to date these changes have not yet been incorporated in 32 CFR 219 or in a DoD directive.⁵³

Special Compensation Programs

There are special DoD programs to provide additional compensation for military research volunteers, including regulations authorizing experimental stress pay. This incentive pay is currently an

additional \$150 per month, whether the service member participates in 1 day of testing or 30 days of testing in any given month.⁵⁴ Two days of testing that include the last day of one month and the first day of the subsequent month would make the test subject eligible for environmental stress pay in both months. The \$150 payment for environmental stress pay may represent the difference in monthly pay between one enlisted pay grade and another. Not all types of military research qualify a volunteer for stress pay however. Only human acceleration or deceleration studies, thermal stress experiments, and high- or low-pressure chamber duty qualify for experimental stress pay. The Navy has specific criteria that apply only to Navy personnel involved in hyperbaric chamber duty and diving. Competent medical authorities make a determination as to whether or not a given study qualifies a service member for experimental stress pay.

Another type of payment for military members involved in military research is payment for blood draws. This law applies to persons donating or furnishing blood at government expense but also pertains to persons who furnish blood for scientific and research purposes as long as the person giving blood does not receive direct benefit.⁵⁵ This code authorizes up to \$50 per blood draw, to be drawn from public funds that are part of the research agency's budget. The head of each department or agency concerned determines payment policies. Some agencies that could pay volunteers for blood draws under this code have decided not to because of insufficient funds in their budget, concerns over creating an unreasonable inducement, and to avoid creating a precedent that would be difficult to maintain in the future for budgetary or other reasons.

If civilians who are not government employees are used as test subjects, payments for their time and inconvenience may be made provided that these payments are not so high as to be coercive. The payments need to be reasonable to cover inconvenience or expenses such as transportation and childcare that the volunteers may incur by participating in the study. They should be comparable to payments for studies at other institutions in the geographical area. The payments should not be so high as to encourage participation for payment only. If payments are withheld until the end of the study and not prorated, this may be a coercive incentive to people who want to withdraw but also want the payment. No regulation requires that the payment schedules to civilian volunteers be approved by the IRB, but it is strongly recommended because the local IRB needs to use their judgment in determining whether or not payments might be coercive.

Advertisements used to recruit civilians should also be IRB approved. Many military IRBs have these requirements as part of their institutional policies. It is always best to get IRB approval for everything involving the conduct of human research and this is especially true when monetary compensation is used.

One item that should be included on the informed consent form when using civilian volunteers in human research is a statement that they will receive medical care should they become injured or ill as a result of their participation. These statements need to be coordinated with local medical providers to be certain that they will provide the care that has been stipulated in the informed consent form. If medical care cannot be guaranteed then civilians should not be used to conduct DoD-funded research. Providing medical care to civilian volunteers is a statement that the Department of the Army has made regarding how it will conduct human research. Individual Army researchers do not have the authority to disregard this policy.

Electronic Data

Advances in computer hardware and software technology have made the use of electronic data much more feasible in recent years. Vast databases of demographic and medical outcomes data can and have been created on desktop computers containing sensitive personal data on millions of service members.⁵⁶ As technology improves, it will become possible to link many different types of data for epidemiological research. This data could include lab results, radiographic images, photographs, pathology specimens, voice, free text, scanned images of records, and genetic material, as well as other potential data sources in the future. Whenever a situation develops that generates great excitement for its research possibilities, it is important that the enthusiasm for expected benefits from the research be tempered with careful consideration of the possible harms to unsuspecting individuals. In most cases, these individuals will have innocently provided information to trusted authorities, unaware of how it may be used in the future. As long as careful review is accomplished and ongoing oversight is ensured, the research potential of linked data can be realized without causing harm to individuals.

An Example of a Military Human Research Program

Based on our personal experiences at SSBCOM and USARIEM, we believe it is possible to recruit soldier volunteers, obtain truly voluntary informed

consent, and meet the needs of investigators requiring a certain number of subjects completing the study in order to get statistically valid results. In the recent past, this program has worked as follows. A Department of the Army civilian employee manages the human research program. Working closely with her are a sergeant first class, a civilian test coordinator, and a military physician who accompanies the recruiting team to conduct physical exams on soldiers who volunteer for the program. A recruiting team conducts quarterly recruiting trips to advanced individual training (AIT) units after getting authority from the US Army Personnel Command (PERSCOM) to recruit a certain number of soldiers from particular military occupational specialties (MOSs) for a 90-day assignment to USARIEM. Since 1991 the team has targeted combat service support MOSs so that women could be included in the research.

After approval from Army PERSCOM is granted, coordination begins with a recruiting visit to a particular post. Briefings are scheduled in the early evening so that the soldiers will not miss training. The team briefs a large audience of soldiers (optimally about 100 if the goal is to recruit 20 soldiers). The team explains the mission of Natick Labs in developing food, clothing, and individual equipment for the soldier. The team explains the rights of research volunteers, testing procedures, methods of measurement, and collecting data and information about upcoming studies. Often a soldier research volunteer accompanies the team to tell first hand what it's like to be a research volunteer at Natick Labs. After potential volunteers have had a chance to ask questions their participation is solicited. The next morning the new volunteers report to the health clinic for a physical exam, usually from the Natick physician that travels with the team. While waiting to see the doctor the soldiers have a chance to ask more questions about the program.

Once soldiers report to the Natick labs, they are greeted by the staff, and then they in-process. They are assigned jobs on post to work when they are not participating in human research studies. By their second or third day they are usually scheduled to attend their first study briefing. The team that recruits the volunteers is also the team that schedules briefings, assigns soldiers to studies, and makes sure that their rights as research volunteers are protected. No one from the research team is a scientist, which minimizes the opportunity for a conflict of interest.

Before their first briefing soldiers are told that the program is entirely voluntary and they do not have to enroll in the study if they do not want to. They may be somewhat hesitant at first but after

they have attended a few briefings and had a chance to interact with the investigators and talk to their fellow soldiers their comfort with the program generally increases. They learn that the team has been honest with them and is genuinely concerned about their rights and welfare.

Soldiers are scheduled to attend study briefings regularly in the climatic chambers building, where the human research program team has its offices. Occasionally briefings are conducted in labs where the research is ongoing to allow the soldiers to see the study actually taking place. This is helpful if elements of the study are difficult to explain in a classroom setting, or when direct observation provides the clearest picture of the demands of the study.

When the investigators are conducting the briefing, a human research program team member is always present as a witness to ensure that the investigator thoroughly explains the study in terms the soldiers can understand. If there is something that might confuse soldiers the witness asks questions to get clarification. Once soldiers see the witness asking questions or other soldiers asking questions



Fig. 19-6. These soldiers are participating in a March 1990 study to determine whether dietary sodium intake is related to acclimatization to extreme desert conditions (120°F and 20% relative humidity). The overhead rigging shown in the photo includes lines for wires and tubes used to collect data on physiologic status. Physicians monitor volunteer participants in such studies for adverse reactions—an important step in assuring their health and well-being. Photograph: Courtesy of US Army Research Institute of Environmental Medicine, Natick, Massachusetts.

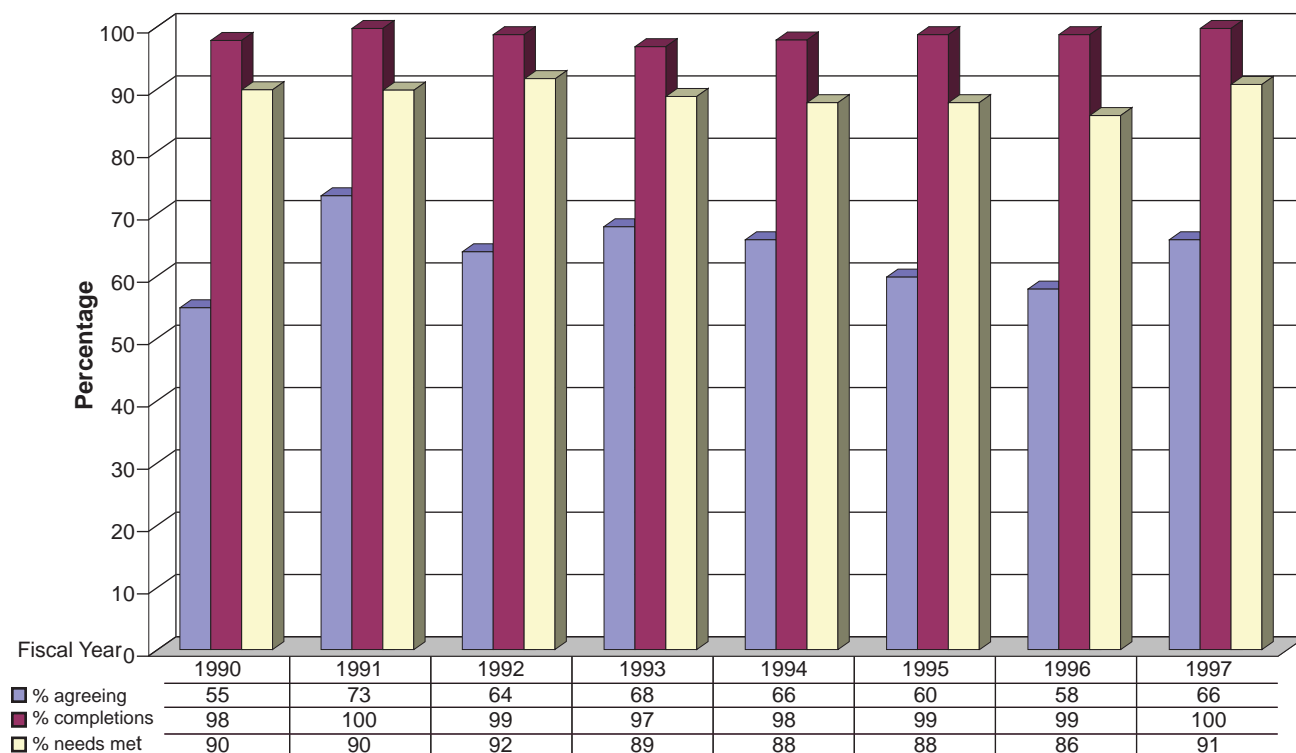


Fig. 19-7. Proportion of soldiers invited to participate in research who volunteer to do so vs. proportion who actually complete the study once enrolled vs. proportion of investigator's needs met.

Note: Soldiers attend multiple informed consent briefings in any given year, and thus have multiple opportunities to participate. Not all soldiers who volunteer for a study are enrolled, however. Data provided by the Human Research Support Program Coordinator, The Soldiers Systems Command, Natick, Massachusetts.

they feel more comfortable asking questions of their own. In most research settings, it is not customary to conduct informed consent briefings in groups. However, this continues to be the preferred method at SSBCOM due to the nature of the research, the benefits of hearing the questions and concerns of other potential volunteers, and the opportunity it affords the individual to make an unpressured decision after the briefing is over and the investigator has departed.

When soldiers sign their consent forms for a study they believe they are signing up to participate in an important research project. They become an important part of the research team. This is one of the main motivational factors because Army research often has no direct benefit for the individual soldier volunteer (Figure 19-6).

The soldier volunteers also have responsibilities once they sign up to do a study, including reading and following the test schedules. Once they volunteer for a study it is their responsibility to report on time to the testing sessions in the correct uniform and to follow any diet or other restrictions proscribed in the research protocol. The soldiers are responsible for letting the investigator or medical monitor know about any changes in their health. Soldiers are also responsible for reporting any study violations. This way any problems that arise can be resolved immediately.

The "voluntariness" of the program is supported by the data. For example, between October 1988 and September 1997, hundreds of volunteer soldiers participated in research at Natick. As shown in Figure 19-7, only an average of 60% to 75% of soldiers briefed on any given study chose to participate. Of those who did volunteer, however, only a small percentage quit before completing the study. The result was that 86% to 92% of the numbers of volunteers requested, on average, were in fact made available for the research. The Natick program supports between 15 and 25 studies annually. Even with rates of refusal running between 25% and 40%, the rate of needs met has been remained fairly consistent over the 8-year period.

Furthermore, the high rate of refusals indicates that soldiers feel comfortable not enrolling in certain studies and is *prima facie* evidence of the voluntary nature of the program. Having some number of drop-outs is consistent with freedom of choice and should be viewed as an expected consequence of a voluntary system. The reason the quit rate is so low may be that soldiers are well informed about perspective studies, feel free not to sign up for studies in the first place, and understand the importance of the service they are providing through their participation. Alternatively,

if no one ever quit then that might suggest that the program is not entirely voluntary.

Indirect pressure has occasionally come from command channels to terminate the assignment of individuals who do not appear to be volunteering often enough. This is not an unexpected reaction in a military environment where the culture does not tolerate anyone who appears to not be performing his or her duties. However, if a research program is truly voluntary, a bell-shaped curve might be expected; a few individuals, for whatever reason, will *never* volunteer (as volunteers it is solely their decision whether or not to participate), and other individuals will volunteer each and every time they are given an opportunity.

It is appropriate to ask soldiers who do not sign up for any studies over a period of several months what their intentions are. If they are no longer interested in participating in research they can then be reassigned to another installation if necessary. Soldiers who no longer wish to participate in research typically ask to be reassigned. Sending a sol-



Fig. 19-8. These soldiers are participating in a November 1990 study to determine physiologic response to the personal protective ensemble. Modern warfare carries the increasing likelihood that enemies will employ biological or chemical agents such as anthrax or nerve gas. Researchers are continually developing garments and equipment that will protect soldiers from these modern threats, although they must be tested to ensure that they do not hinder the soldier's mission by limiting dexterity or by placing the wearer at risk of heat exhaustion. The timely development of such garments has the potential to protect soldiers from hostile threats on the battlefield, but researchers face an ethical imperative to ensure the safety of the soldiers who assist in the development of such protective equipment. Photograph: Courtesy of US Army Research Institute of Environmental Medicine, Natick, Massachusetts.

dier (who desires to move on) to a new duty assignment does not represent an adverse consequence because it has been a standard practice to reassign personnel based on the needs of the military services for decades. Forcing a person to move solely based upon their unwillingness to volunteer for studies, however, is inconsistent with a truly voluntary program.

Even though soldiers volunteer to come to Natick for 90 days, many of these soldiers like the testing so much that they request to stay an additional 90 days. These extension requests have to be approved by PERSCOM. Extending soldier volunteers has been a very cost effective way of ensuring a pool of enthusiastic potential volunteers is available for studies.

In the recent past, Natick was also authorized to recruit 15 soldiers who were assigned as research volunteers for 2 years. This group of so-called permanent party volunteers has formed the backbone of the Natick program. It is difficult to recruit during the summer months because that is when the

reservists and National Guard soldiers are trained. Because Natick only recruits Regular Army soldiers and because the permanent party group is continually available to volunteer for studies during summer months and during lags between the recruitment of new soldiers, this group has contributed great stability to the volunteer pool.

When soldiers are not testing they work in a job on post that best utilizes their individual occupational skills and interests. SSBCOM Headquarters Detachment provides military training and physical fitness programs and monitoring for the research soldier-volunteers. In this way, the Army can meet the military career needs of the volunteers while supporting a wide spectrum of important militarily relevant human research. The Natick program is successful because the soldier volunteers, scientists, military chain of command, and human research support program office all work together to protect the rights of the soldiers while these militarily important research protocols are being conducted (Figure 19-8).

CONCLUSION

The most important way to improve human research within the DoD is to educate commanders and investigators alike about the rights of soldier research volunteers. This is difficult because most of the military is not involved with research on a daily basis and the very notion of “volunteer” may run counter to traditional military thinking. It should be a requirement when human research is conducted in field units that unit commanders be briefed as to the voluntary nature of human research as described in the Code of Federal Regulations and in each service’s specific regulations.

Military organizations that are involved in developing, testing, and evaluating materials and equipment for use by soldiers, marines, sailors, and airmen should fully understand the military’s human use policies and regulations. Even though they may not be conducting human research per se, they often involve humans in evaluating the products they are developing, and at these times human research regulations may apply. The military medical community must remain fully informed and compliant with human use regulations if they are to appropriately use soldiers, sailors, marines, and airmen as volunteers for research.

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CHAPTER 19: ATTACHMENT 1

THE BELMONT REPORT

Office of the Secretary

Ethical Principles and Guidelines for the Protection of Human Subjects of Research

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

April 18, 1979

AGENCY: Department of Health, Education, and Welfare [DHEW].

ACTION: Notice of Report for Public Comment.

SUMMARY: On July 12, 1974, the National Research Act (Pub. L. 93-348) was signed into law, thereby creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the charges to the Commission was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and to develop guidelines which should be followed to assure that such research is conducted in accordance with those principles. In carrying out the above, the Commission was directed to consider: (i) the boundaries between biomedical and behavioral research and the accepted and routine practice of medicine, (ii) the role of assessment of risk-benefit criteria in the determination of the appropriateness of research involving human subjects, (iii) appropriate guidelines for the selection of human subjects for participation in such research and (iv) the nature and definition of informed consent in various research settings.

The Belmont Report attempts to summarize the basic ethical principles identified by the Commission in the course of its deliberations. It is the outgrowth of an intensive four-day period of discussions that were held in February 1976 at the Smithsonian Institution's Belmont Conference Center supplemented by the monthly deliberations of the Commission that were held over a period of nearly four years. It is a statement of basic ethical principles and guidelines that should assist in resolving the ethical problems that surround the conduct of research with human subjects. By publishing the Report in the Federal Register, and providing reprints upon request, the Secretary intends that it may be made readily available to scientists, members of Institutional Review Boards, and Federal employees. The two-volume Appendix, containing the lengthy reports of experts and specialists who assisted the Commission in fulfilling this part of its charge, is available as DHEW Publication No. (OS) 78-0013 and No. (OS) 78-0014, for sale by the Superintendent of Documents, US Government Printing Office, Washington, DC 20402.

Unlike most other reports of the Commission, the Belmont Report does not make specific recommendations for administrative action by the Secretary of Health, Education, and Welfare. Rather, the Commission recommended that the Belmont Report be adopted in its entirety, as a statement of the Department's policy. The Department requests public comment on this recommendation.

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

Members of the Commission

Kenneth John Ryan, MD, Chairman, Chief of Staff, Boston Hospital for Women.

Joseph V. Brady, PhD, Professor of Behavioral Biology, Johns Hopkins University.

Robert E. Cooke, MD, President, Medical College of Pennsylvania.

Dorothy I. Height, President, National Council of Negro Women, Inc.

Albert R. Jonsen, PhD, Associate Professor of Bioethics, University of California at San Francisco.

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Table of Contents

Ethical Principles and Guidelines for Research Involving Human Subjects

- A. Boundaries Between Practice and Research
- B. Basic Ethical Principles
 - 1. Respect for Persons
 - 2. Beneficence
 - 3. Justice
- C. Applications
 - 1. Informed Consent
 - 2. Assessment of Risk and Benefits
 - 3. Selection of Subjects

Ethical Principles & Guidelines for Research Involving Human Subjects

Scientific research has produced substantial social benefits. It has also posed some troubling ethical questions. Public attention was drawn to these questions by reported abuses of human subjects in biomedical experiments, especially during the Second World War. During the Nuremberg War Crime Trials, the Nuremberg code was drafted as a set of standards for judging physicians and scientists who had conducted biomedical experiments on concentration camp prisoners. This code became the prototype of many later codes¹ intended to assure that research involving human subjects would be carried out in an ethical manner.

The codes consist of rules, some general, others specific, that guide the investigators or the reviewers of research in their work. Such rules often are inadequate to cover complex situations; at times they come into conflict, and they are frequently difficult to interpret or apply. Broader ethical principles will provide a basis on which specific rules may be formulated, criticized and interpreted.

Three principles, or general prescriptive judgments, that are relevant to research involving human subjects are identified in this statement. Other principles may also be relevant. These three are comprehensive, however, and are stated at a level of generalization that should assist scientists, subjects, reviewers and interested citizens to understand the ethical issues inherent in research involving human subjects. These principles cannot always be applied so as to resolve beyond dispute particular ethical problems. The objective is to provide an analytical framework that will guide the resolution of ethical problems arising from research involving human subjects.

This statement consists of a distinction between research and practice, a discussion of the three basic ethical principles, and remarks about the application of these principles.

A. Boundaries Between Practice and Research

It is important to distinguish between biomedical and behavioral research, on the one hand, and the practice of accepted therapy on the other, in order to know what activities ought to undergo review for the protection of human subjects of research. The distinction between research and practice is blurred partly because both often occur together (as in research designed to evaluate a therapy) and partly because notable departures from standard practice are often called “experimental” when the terms “experimental” and “research” are not carefully defined.

For the most part, the term “practice” refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals.² By contrast, the term “research” designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective.

When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is “experimental,” in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective. Thus, it is the responsibility of medical practice committees, for example, to insist that a major innovation be incorporated into a formal research project.³

Research and practice may be carried on together when research is designed to evaluate the safety and efficacy of a therapy. This need not cause any confusion regarding whether or not the activity requires review; the general rule is that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects.

B. Basic Ethical Principles

The expression “basic ethical principles” refers to those general judgments that serve as a basic justification for the many particular ethical prescriptions and evaluations of human actions. Three basic principles, among those generally accepted in our cultural tradition, are particularly relevant to the ethics of research involving human subjects: the principles of respect of persons, beneficence and justice.

1. Respect for Persons. Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy.

An autonomous person is an individual capable of deliberation about personal goals and of acting under the direction of such deliberation. To respect autonomy is to give weight to autonomous persons’ considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others. To show lack of respect for an autonomous agent is to repudiate that person’s considered judgments, to deny an individual the freedom to act on those considered judgments, or to withhold information necessary to make a considered judgment, when there are no compelling reasons to do so.

However, not every human being is capable of self-determination. The capacity for self-determination matures

during an individual's life, and some individuals lose this capacity wholly or in part because of illness, mental disability, or circumstances that severely restrict liberty. Respect for the immature and the incapacitated may require protecting them as they mature or while they are incapacitated.

Some persons are in need of extensive protection, even to the point of excluding them from activities which may harm them; other persons require little protection beyond making sure they undertake activities freely and with awareness of possible adverse consequence. The extent of protection afforded should depend upon the risk of harm and the likelihood of benefit. The judgment that any individual lacks autonomy should be periodically reevaluated and will vary in different situations.

In most cases of research involving human subjects, respect for persons demands that subjects enter into the research voluntarily and with adequate information. In some situations, however, application of the principle is not obvious. The involvement of prisoners as subjects of research provides an instructive example. On the one hand, it would seem that the principle of respect for persons requires that prisoners not be deprived of the opportunity to volunteer for research. On the other hand, under prison conditions they may be subtly coerced or unduly influenced to engage in research activities for which they would not otherwise volunteer. Respect for persons would then dictate that prisoners be protected. Whether to allow prisoners to "volunteer" or to "protect" them presents a dilemma. Respecting persons, in most hard cases, is often a matter of balancing competing claims urged by the principle of respect itself.

2. Beneficence. Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. Such treatment falls under the principle of beneficence. The term "beneficence" is often understood to cover acts of kindness or charity that go beyond strict obligation. In this document, beneficence is understood in a stronger sense, as an obligation. Two general rules have been formulated as complementary expressions of beneficent actions in this sense: (1) do not harm and (2) maximize possible benefits and minimize possible harms.

The Hippocratic maxim "do no harm" has long been a fundamental principle of medical ethics. Claude Bernard extended it to the realm of research, saying that one should not injure one person regardless of the benefits that might come to others. However, even avoiding harm requires learning what is harmful; and, in the process of obtaining this information, persons may be exposed to risk of harm. Further, the Hippocratic Oath requires physicians to benefit their patients "according to their best judgment." Learning what will in fact benefit may require exposing persons to risk. The problem posed by these imperatives is to decide when it is justifiable to seek certain benefits despite the risks involved, and when the benefits should be foregone because of the risks.

The obligations of beneficence affect both individual investigators and society at large, because they extend both to particular research projects and to the entire enterprise of research. In the case of particular projects, investigators and members of their institutions are obliged to give forethought to the maximization of benefits and the reduction of risk that might occur from the research investigation. In the case of scientific research in general, members of the larger society are obliged to recognize the longer term benefits and risks that may result from the improvement of knowledge and from the development of novel medical, psychotherapeutic, and social procedures.

The principle of beneficence often occupies a well-defined justifying role in many areas of research involving human subjects. An example is found in research involving children. Effective ways of treating childhood diseases and fostering healthy development are benefits that serve to justify research involving children—even when individual research subjects are not direct beneficiaries. Research also makes it possible to avoid the harm that may result from the application of previously accepted routine practices that on closer investigation turn out to be dangerous. But the role of the principle of beneficence is not always so unambiguous. A difficult ethical problem remains, for example, about research that presents more than minimal risk without immediate prospect of direct benefit to the children involved. Some have argued that such research is inadmissible, while others have pointed out that this limit would rule out much research promising great benefit to children in the future. Here again, as with all hard cases, the different claims covered by the principle of beneficence may come into conflict and force difficult choices.

3. Justice. Who ought to receive the benefits of research and bear its burdens? This is a question of justice, in the sense of "fairness in distribution" or "what is deserved." An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly. Another way of conceiving the principle of justice is that equals ought to be treated equally. However, this statement requires explication. Who is equal and who is unequal? What considerations justify departure from equal distribution? Almost all commentators allow that distinctions based on experience, age, deprivation, competence, merit and position do sometimes constitute criteria justifying differential treatment for certain purposes. It is necessary, then, to explain in what respects people should be treated equally. There are several widely accepted formulations of just ways to distribute burdens and benefits. Each formulation mentions some relevant property on the basis of which burdens and benefits should be distributed. These formulations are (1) to each person an equal share, (2) to each person according to individual need, (3) to each person according to individual effort, (4) to each person according to societal contribution, and (5) to each person according to merit.

Questions of justice have long been associated with social practices such as punishment, taxation and political

representation. Until recently these questions have not generally been associated with scientific research. However, they are foreshadowed even in the earliest reflections on the ethics of research involving human subjects. For example, during the 19th and early 20th centuries the burdens of serving as research subjects fell largely upon poor ward patients, while the benefits of improved medical care flowed primarily to private patients. Subsequently, the exploitation of unwilling prisoners as research subjects in Nazi concentration camps was condemned as a particularly flagrant injustice. In this country, in the 1940s, the Tuskegee syphilis study used disadvantaged, rural black men to study the untreated course of a disease that is by no means confined to that population. These subjects were deprived of demonstrably effective treatment in order not to interrupt the project, long after such treatment became generally available.

Against this historical background, it can be seen how conceptions of justice are relevant to research involving human subjects. For example, the selection of research subjects needs to be scrutinized in order to determine whether some classes (eg, welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied. Finally, whenever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands both that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.

C. Applications

Applications of the general principles to the conduct of research leads to consideration of the following requirements: informed consent, risk/benefit assessment, and the selection of subjects of research.

1. Informed Consent. Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed consent are satisfied.

While the importance of informed consent is unquestioned, controversy prevails over the nature and possibility of an informed consent. Nonetheless, there is widespread agreement that the consent process can be analyzed as containing three elements: information, comprehension and voluntariness.

Information. Most codes of research establish specific items for disclosure intended to assure that subjects are given sufficient information. These items generally include: the research procedure, their purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research. Additional items have been proposed, including how subjects are selected, the person responsible for the research, etc.

However, a simple listing of items does not answer the question of what the standard should be for judging how much and what sort of information should be provided. One standard frequently invoked in medical practice, namely the information commonly provided by practitioners in the field or in the locale, is inadequate since research takes place precisely when a common understanding does not exist. Another standard, currently popular in malpractice law, requires the practitioner to reveal the information that reasonable persons would wish to know in order to make a decision regarding their care. This, too, seems insufficient since the research subject, being in essence a volunteer, may wish to know considerably more about risks gratuitously undertaken than do patients who deliver themselves into the hand of a clinician for needed care. It may be that a standard of "the reasonable volunteer" should be proposed: the extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge. Even when some direct benefit to them is anticipated, the subjects should understand clearly the range of risk and the voluntary nature of participation.

A special problem of consent arises where informing subjects of some pertinent aspect of the research is likely to impair the validity of the research. In many cases, it is sufficient to indicate to subjects that they are being invited to participate in research of which some features will not be revealed until the research is concluded. In all cases of research involving incomplete disclosure, such research is justified only if it is clear that (1) incomplete disclosure is truly necessary to accomplish the goals of the research, (2) there are no undisclosed risks to subjects that are more than minimal, and (3) there is an adequate plan for debriefing subjects, when appropriate, and for dissemination of research results to them. Information about risks should never be withheld for the purpose of eliciting the cooperation of subjects, and truthful answers should always be given to direct questions about the research. Care should be taken to distinguish cases in which disclosure would destroy or invalidate the research from cases in which disclosure would simply inconvenience the investigator.

Comprehension. The manner and context in which information is conveyed is as important as the information itself. For example, presenting information in a disorganized and rapid fashion, allowing too little time for consideration or curtailing opportunities for questioning, all may adversely affect a subject's ability to make an informed choice.

Because the subject's ability to understand is a function of intelligence, rationality, maturity and language, it is necessary to adapt the presentation of the information to the subject's capacities. Investigators are responsible for ascertaining that the subject has comprehended the information. While there is always an obligation to ascertain that

the information about risk to subjects is complete and adequately comprehended, when the risks are more serious, that obligation increases. On occasion, it may be suitable to give some oral or written tests of comprehension.

Special provision may need to be made when comprehension is severely limited—for example, by conditions of immaturity or mental disability. Each class of subjects that one might consider as incompetent (eg, infants and young children, mentally disable patients, the terminally ill and the comatose) should be considered on its own terms. Even for these persons, however, respect requires giving them the opportunity to choose to the extent they are able, whether or not to participate in research. The objections of these subjects to involvement should be honored, unless the research entails providing them a therapy unavailable elsewhere. Respect for persons also requires seeking the permission of other parties in order to protect the subjects from harm. Such persons are thus respected both by acknowledging their own wishes and by the use of third parties to protect them from harm.

The third parties chosen should be those who are most likely to understand the incompetent subject's situation and to act in that person's best interest. The person authorized to act on behalf of the subject should be given an opportunity to observe the research as it proceeds in order to be able to withdraw the subject from the research, if such action appears in the subject's best interest.

Voluntariness. An agreement to participate in research constitutes a valid consent only if voluntarily given. This element of informed consent requires conditions free of coercion and undue influence. Coercion occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance. Undue influence, by contrast, occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance. Also, inducements that would ordinarily be acceptable may become undue influences if the subject is especially vulnerable.

Unjustifiable pressures usually occur when persons in positions of authority or commanding influence—especially where possible sanctions are involved—urge a course of action for a subject. A continuum of such influencing factors exists, however, and it is impossible to state precisely where justifiable persuasion ends and undue influence begins. But undue influence would include actions such as manipulating a person's choice through the controlling influence of a close relative and threatening to withdraw health services to which an individual would otherwise be entitled.

2. Assessment of Risks and Benefits. The assessment of risks and benefits requires a careful array of relevant data, including, in some cases, alternative ways of obtaining the benefits sought in the research. Thus, the assessment presents both an opportunity and a responsibility to gather systematic and comprehensive information about proposed research. For the investigator, it is a means to examine whether the proposed research is properly designed. For a review committee, it is a method for determining whether the risks that will be presented to subjects are justified. For prospective subjects, the assessment will assist the determination whether or not to participate.

The Nature and Scope of Risks and Benefits. The requirement that research be justified on the basis of a favorable risk/benefit assessment bears a close relation to the principle of beneficence, just as the moral requirement that informed consent be obtained is derived primarily from the principle of respect for persons. The term "risk" refers to a possibility that harm may occur. However, when expressions such as "small risk" or "high risk" are used, they usually refer (often ambiguously) both to the chance (probability) of experiencing a harm and the severity (magnitude) of the envisioned harm.

The term "benefit" is used in the research context to refer to something of positive value related to health or welfare. Unlike, "risk," "benefit" is not a term that expresses probabilities. Risk is properly contrasted to probability of benefits, and benefits are properly contrasted with harms rather than risks of harm. Accordingly, so-called risk/benefit assessments are concerned with the probabilities and magnitudes of possible harm and anticipated benefits. Many kinds of possible harms and benefits need to be taken into account. There are, for example, risks of psychological harm, physical harm, legal harm, social harm and economic harm and the corresponding benefits. While the most likely types of harms to research subjects are those of psychological or physical pain or injury, other possible kinds should not be overlooked.

Risks and benefits of research may affect the individual subjects, the families of the individual subjects, and society at large (or special groups of subjects in society). Previous codes and Federal regulations have required that risks to subjects be outweighed by the sum of both the anticipated benefit to the subject, if any, and the anticipated benefit to society in the form of knowledge to be gained from the research. In balancing these different elements, the risks and benefits affecting the immediate research subject will normally carry special weight. On the other hand, interests other than those of the subject may on some occasions be sufficient by themselves to justify the risks involved in the research, so long as the subjects' rights have been protected. Beneficence thus requires that we protect against risk of harm to subjects and also that we be concerned about the loss of the substantial benefits that might be gained from research.

The Systematic Assessment of Risks and Benefits. It is commonly said that benefits and risks must be "balanced" and shown to be "in a favorable ratio." The metaphorical character of these terms draws attention to the difficulty of making precise judgments. Only on rare occasions will quantitative techniques be available for the scrutiny of research protocols. However, the idea of systematic, nonarbitrary analysis of risks and benefits should be emulated insofar as possible. This ideal requires those making decisions about the justifiability of research to be thorough in the accumulation and assessment of information about all aspects of the research, and to consider alternatives systematically. This procedure renders the assessment of research more rigorous and precise, while making

communication between review board members and investigators less subject to misinterpretation, misinformation and conflicting judgments. Thus, there should first be a determination of the validity of the presuppositions of the research; then the nature, probability and magnitude of risk should be distinguished with as much clarity as possible. The method of ascertaining risks should be explicit, especially where there is no alternative to the use of such vague categories as small or slight risk. It should also be determined whether an investigator's estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies.

Finally, assessment of the justifiability of research should reflect at least the following considerations: (i) Brutal or inhumane treatment of human subjects is never morally justified. (ii) Risks should be reduced to those necessary to achieve the research objective. It should be determined whether it is in fact necessary to use human subjects at all. Risk can perhaps never be entirely eliminated, but it can often be reduced by careful attention to alternative procedures. (iii) When research involves significant risk of serious impairment, review committees should be extraordinarily insistent on the justification of the risk (looking usually to the likelihood of benefit to the subject—or, in some rare cases, to the manifest voluntariness of the participation). (iv) When vulnerable populations are involved in research, the appropriateness of involving them should itself be demonstrated. A number of variables go into such judgments, including the nature and degree of risk, the condition of the particular population involved, and the nature and level of the anticipated benefits. (v) Relevant risks and benefits must be thoroughly arrayed in documents and procedures used in the informed consent process.

3. Selection of Subjects. Just as the principle of respect for persons finds expression in the requirements for consent, and the principle of beneficence in risk/benefit assessment, the principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects.

Justice is relevant to the selection of subjects of research at two levels: the social and the individual. Individual justice in the selection of subjects would require that researchers exhibit fairness: thus, they should not offer potentially beneficial research only to some patients who are in their favor or select only "undesirable" persons for risky research. Social justice requires that distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens and on the appropriateness of placing further burdens on already burdened persons. Thus, it can be considered a matter of social justice that there is an order of preference in the selection of classes of subjects (eg, adults before children) and that some classes of potential subjects (eg, the institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions.

Injustice may appear in the selection of subjects, even if individual subjects are selected fairly by investigators and treated fairly in the course of research. Thus injustice arises from social, racial, sexual and cultural biases institutionalized in society. Thus, even if individual researchers are treating their research subjects fairly, and even if IRBs are taking care to assure that subjects are selected fairly within a particular institution, unjust social patterns may nevertheless appear in the overall distribution of the burdens and benefits of research. Although individual institutions or investigators may not be able to resolve a problem that is pervasive in their social setting, they can consider distributive justice in selecting research subjects.

Some populations, especially institutionalized ones, are already burdened in many ways by their infirmities and environments. When research is proposed that involves risks and does not include a therapeutic component, other less burdened classes of persons should be called upon first to accept these risks of research, except where the research is directly related to the specific conditions of the class involved. Also, even though public funds for research may often flow in the same directions as public funds for health care, it seems unfair that populations dependent on public health care constitute a pool of preferred research subjects if more advantaged populations are likely to be the recipients of the benefits.

One special instance of injustice results from the involvement of vulnerable subjects. Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized may continually be sought as research subjects, owing to their ready availability in settings where research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition.

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Endnotes:

1. Since 1945, various codes for the proper and responsible conduct of human experimentation in medical research have been adopted by different organizations. The best known of these codes are the Nuremberg Code of 1947, the Helsinki Declaration of 1964 (revised in 1975), and the 1971 Guidelines (codified into Federal Regulations in 1974) issued by the US Department of Health, Education, and Welfare. Codes for the conduct of social and behavioral research have also been adopted, the best known being that of the Ameri-

- can Psychological Association, published in 1973.
2. Although practice usually involves interventions designed solely to enhance the well-being of a particular individual, interventions are sometimes applied to one individual for the enhancement of the well-being of another (eg, blood donation, skin grafts, organ transplants) or an intervention may have the dual purpose of enhancing the well-being of a particular individual, and, at the same time, providing some benefit to others (eg, vaccination, which protects both the person who is vaccinated and society generally). The fact that some forms of practice have elements other than immediate benefit to the individual receiving an intervention, however, should not confuse the general distinction between research and practice. Even when a procedure applied in practice may benefit some other person, it remains an intervention designed to enhance the well-being of a particular individual or groups of individuals; thus, it is practice and need not be reviewed as research.
 3. Because the problems related to social experimentation may differ substantially from those of biomedical and behavioral research, the Commission specifically declines to make any policy determination regarding such research at this time. Rather, the Commission believes that the problem ought to be addressed by one of its successor bodies.

Available at: <http://ohrp.osophs.dhhs.gov/humansubjects/guidance/belmont.htm>. Accessed 23 April 2002; formatted to *Text-books of Military Medicine* style.

CHAPTER 19: ATTACHMENT 2

1991 INTERNATIONAL GUIDELINES FOR ETHICAL REVIEW OF EPIDEMIOLOGICAL STUDIES

INTRODUCTION

These Guidelines are intended for investigators, health policy-makers, members of ethical review committees, and others who have to deal with ethical issues that arise in epidemiology. They may also assist in the establishment of standards for ethical review of epidemiological studies.

The Guidelines are an expression of concern to ensure that epidemiological studies observe ethical standards. These standards apply to all who undertake any of the types of activity covered by the Guidelines. Investigators must always be held responsible for the ethical integrity of their studies.

Epidemiology is defined as the study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to control of health problems.

Epidemiology has greatly improved the human condition in the present century. It has clarified our understanding of many physical, biological and behavioural dangers to health. Some of the knowledge obtained has been applied to the control of environmental and biological threats to health, such as diseases due to drinking polluted water. Other epidemiological knowledge has become part of popular culture, leading to changed values and behaviour, and thus has led to improved health: examples include attitudes towards personal hygiene, tobacco smoking, diet and exercise in relation to heart disease, and the use of seat-belts to reduce the risk of traffic injury and death.

Epidemiological practice and research are based mostly on observation, and require no intervention more invasive than asking questions and carrying out routine medical examinations. Practice and research may overlap, as, for example, when both routine surveillance of cancer and original research on cancer are conducted by professional staff of a population-based cancer registry.

Epidemiological research is of two main types: observational and experimental:

Three types of observational epidemiological research are distinguished: *cross-sectional studies* (also known as surveys), *case-control studies*, and *cohort studies*. These types of study carry minimal risk to study subjects. They involve no intervention other than asking questions, carrying out medical examinations and, sometimes, laboratory tests or x-ray examinations. The informed consent of subjects is normally required, although there are some exceptions—for example, very large cohort studies conducted exclusively by examining medical records.

A *cross-sectional study* (survey) is commonly done on a random sample of a population. Study subjects are asked questions, medically examined, or asked to submit to laboratory tests. Its aim is to assess aspects of the health of a population, or to test hypotheses about possible causes of disease or suspected risk factors.

A *case-control study* compares the past history of exposure to risk among patients who have a specified condition (cases) with the past history of exposure to this risk among persons who resemble the cases in such respects as age and sex, but do not have the specified condition (controls). Differing frequency of past exposure among cases and controls can be statistically analysed to test hypotheses about causes or risk factors. Case-control studies are the method of choice for testing hypotheses about rare conditions, because they can be done with small numbers of cases. They generally do not involve invasion of privacy or violation of confidentiality. If a case-control study requires direct contact between research workers and study subjects, informed consent to participation in the study is required; if it entails only a review of medical records, informed consent may not be required and indeed may not be feasible.

In a *cohort study*, also known as a longitudinal or prospective study, individuals with differing exposure levels to suspected risk factors are identified and observed over a period, commonly years, and the rates of occurrence of the condition of interest are measured and compared in relation to exposure levels. This is a more robust research method than a cross-sectional or case-control study, but it requires study of large numbers for a long time and is costly. Usually it requires only asking questions and routine medical examinations; sometimes it requires laboratory tests. Informed consent is normally required, but an exception to this requirement is a retrospective cohort study that uses linked medical records. In a retrospective cohort study, the initial or base-line observations may relate to exposure many years earlier to a potentially harmful agent, such as x-rays, a prescribed drug or an occupational hazard, about which details are known; the final or endpoint observations are often obtained from death certificates. Numbers of subjects may be very large, perhaps millions, so it would be impracticable to obtain their informed consent. It is essential to identify precisely every individual studied; this is achieved by methods of matching that are built into record linkage systems. After identities have been established to compile the statistical tables, all personal identifying information is obliterated, and therefore privacy and confidentiality are safeguarded.

An experiment is a study in which the investigator intentionally alters one or more factors under controlled conditions to study the effects of doing so. The usual form of epidemiological experiment is the *randomized controlled trial*, which is done to test a preventive or therapeutic regimen or diagnostic procedure. Such experiments involving human subjects should be regarded as unethical unless there is genuine uncertainty about the regimen or procedure and this uncertainty can be clarified by research.

Usually in this form of experiment, subjects are allocated at random to groups, one group to receive, the other group not to receive, the experimental regimen or procedure. The experiment compares the outcomes in the two groups. Random allocation removes the effects of bias, which would destroy the validity of comparisons between the groups. Since it is always possible that harm may be caused to at least some of the subjects, their informed consent is essential.

Epidemiology is facing new challenges and opportunities. The application of information technology to large data-files has expanded the role and capacity of epidemiological studies. The acquired immunodeficiency syndrome (AIDS) epidemic and its management have given epidemiological studies new urgency; public health authorities are using population-screening studies to establish prevalence levels of human immunodeficiency virus (HIV) infection for purposes of monitoring and restricting the spread of infection. Ahead lie entirely new challenges, such as those arising from the conjunction of molecular and population genetics.

PREAMBLE

The general conduct of biomedical studies is guided by statements of internationally recognized principles of human rights, including the Nuremberg Code and the World Medical Association's Declaration of Helsinki, as revised (Helsinki IV). These principles also underlie the Proposed International Guidelines for Biomedical Research Involving Human Subjects, issued by the Council for International Organizations of Medical Sciences in 1982. These and similar national codes are based on the model of clinical medicine, and often address interests of "patients" or individual "subjects." Epidemiological research concerns groups of people, and the above codes do not adequately cover its special features. Proposals for epidemiological studies should be reviewed independently on ethical grounds.

Ethical issues often arise as a result of conflict among competing sets of values, such as, in the field of public health, the conflict between the rights of individuals and the needs of communities. Adherence to these guidelines will not avoid all ethical problems in epidemiological studies. Many situations require careful discussion and informed judgement on the part of investigators, ethical review committees, administrators, health-care practitioners, policy-makers, and community representatives. Externally sponsored epidemiological studies in developing countries merit special attention. A framework for the application of these guidelines is set by the laws and practices in each jurisdiction in which it is proposed to undertake studies.

The purpose of ethical review is to consider the features of a proposed study in the light of ethical principles, so as to ensure that investigators have anticipated and satisfactorily resolved possible ethical objections, and to assess their responses to ethical issues raised by the study. Not all ethical principles weigh equally. A study may be assessed as ethical even if a usual ethical expectation, such as confidentiality of data, has not been comprehensively met, provided the potential benefits clearly outweigh the risks and the investigators give assurances of minimizing risks. It may even be unethical to reject such a study, if its rejection would deny a community the benefits it offers. The challenge of ethical review is to make assessments that take into account potential risks and benefits, and to reach decisions on which members of ethical review committees may reasonably differ.

Different conclusions may result from different ethical reviews of the same issue or proposal, and each conclusion may be ethically reached, given varying circumstances of place and time; a conclusion is ethical not merely because of what has been decided but also owing to the process of conscientious reflection and assessment by which it has been reached.

GENERAL ETHICAL PRINCIPLES

All research involving human subjects should be conducted in accordance with four basic ethical principles, namely *respect for persons*, *beneficence*, *non-maleficence*, and *justice*. It is usually assumed that these principles guide the conscientious preparation of proposals for scientific studies. In varying circumstances, they may be expressed differently and given different weight, and their application, in all good faith, may have different effects and lead to different decisions or courses of action. These principles have been much discussed and clarified in recent decades, and it is the aim of these Guidelines that they be applied to epidemiology.

Respect for persons incorporates at least two other fundamental ethical principles, namely:

- (a) *autonomy*, which requires that those who are capable of deliberation about their personal goals should be treated with respect for their capacity for self-determination; and
- (b) *protection of persons* with impaired or diminished autonomy, which requires that those who are dependent or vulnerable be afforded security against harm or abuse.

Beneficence is the ethical obligation to maximize possible benefits and to minimize possible harms and wrongs. This principle gives rise to norms requiring that the risks of research be reasonable in the light of the expected benefits, that the research design be sound, and that the investigators be competent both to conduct the research and to assure the well-being of the research subjects.

Non-maleficence ("Do no harm") holds a central position in the tradition of medical ethics, and guards against

avoidable harm to research subjects.

Justice requires that cases considered to be alike be treated alike, and that cases considered to be different be treated in ways that acknowledge the difference. When the principle of justice is applied to dependent or vulnerable subjects, its main concern is with the rules of *distributive justice*. Studies should be designed to obtain knowledge that benefits the class of persons of which the subjects are representative: the class of persons bearing the burden should receive an appropriate benefit, and the class primarily intended to benefit should bear a fair proportion of the risks and burdens of the study.

The rules of distributive justice are applicable within and among communities. Weaker members of communities should not bear disproportionate burdens of studies from which all members of the community are intended to benefit, and more dependent communities and countries should not bear disproportionate burdens of studies from which all communities or countries are intended to benefit. General ethical principles may be applied at individual and community levels. At the level of the individual (*microethics*), ethics governs how one person should relate to another and the moral claims of each member of a community. At the level of the community, ethics applies to how one community relates to another, and to how a community treats each of its members (including prospective members) and members of other groups with different cultural values (*macroethics*). Procedures that are unethical at one level cannot be justified merely because they are considered ethically acceptable at the other.

ETHICAL PRINCIPLES APPLIED TO EPIDEMIOLOGY

Informed Consent

Individual Consent

1. When individuals are to be subjects of epidemiological studies, their informed consent will usually be sought. For epidemiological studies that use personally identifiable private data, the rules for informed consent vary, as discussed further below. Consent is informed when it is given by a person who understands the purpose and nature of the study, what participation in the study requires the person to do and to risk, and what benefits are intended to result from the study.

2. An investigator who proposes not to seek informed consent has the obligation to explain to an ethical review committee how the study would be ethical in its absence: it may be impractical to locate subjects whose records are to be examined, or the purpose of some studies would be frustrated—for example, prospective subjects on being informed would change the behaviour that it is proposed to study, or might feel needlessly anxious about why they were subjects or study. The investigator will provide assurances that strict safeguards will be maintained to protect confidentiality and that the study is aimed at protecting or advancing health. Another justification for not seeking informed consent may be that subjects are made aware through public announcements that it is customary to make personal data available for epidemiological studies.

3. An ethical issue may arise when occupational records, medical records, tissue samples, etc. are used for a purpose for which consent was not given, although the study threatens no harm. Individuals or their public representatives should normally be told that their data might be used in epidemiological studies, and what means of protecting confidentiality are provided. Consent is not required for use of publicly available information, although countries and communities differ with regard to the definition of what information about citizens is regarded as public. However, when such information is to be used, it is understood that investigators will minimize disclosure of personally sensitive information.

4. Some organizations and government agencies employ epidemiologists who may be permitted by legislation or employees' contracts to have access to data without subjects' consent. These epidemiologists must then consider whether it is ethical for them, in a given case, to use this power of access to personal data. Ethically, they may still be expected either to seek the consent of the individuals concerned, or to justify their access without such consent. Access may be ethical on such grounds as minimal risk of harm to individuals, public benefit, and investigators' protection of the confidentiality of the individuals whose data they study.

Community Agreement

5. When it is not possible to request informed consent from every individual to be studied, the agreement of a representative of a community or group may be sought, but the representative should be chosen according to the nature, traditions and political philosophy of the community or group. Approval given by a community representative should be consistent with general ethical principles. When investigators work with communities, they will consider communal rights and protection as they would individual rights and protection. For communities in which collective decision-making is customary, communal leaders can express the collective will. However, the refusal of individuals to participate in a study has to be respected: a leader may express agreement on behalf of a community, but an individual's refusal of personal participation is binding.

6. When people are appointed by agencies outside a group, such as a department of government, to speak for members of the group, investigators and ethical review committees should consider how authentically these people speak for the group, and if necessary seek also the agreement of other representatives. Representatives of a community or group may sometimes be in a position to participate in designing the study and in its ethical assessment.

7. The definition of a community or group for purposes of epidemiological study may be a matter of ethical concern. When members of a community are naturally conscious of its activities as a community and feel common interests with other members, the community exists, irrespective of the study proposal. Investigators will be sensitive to how a community is constituted or defines itself, and will respect the rights of underprivileged groups.

8. For purposes of epidemiological study, investigators may define groups that are composed of statistically, geographically or otherwise associated individuals who do not normally interact socially. When such groups are artificially created for scientific study, group members may not readily be identifiable as leaders or representatives, and individuals may not be expected to risk disadvantage for the benefit of others. Accordingly, it will be more difficult to ensure group representation, and all the more important to obtain subjects' free and informed consent to participate.

Selective Disclosure of Information

9. In epidemiology, an acceptable study technique involves selective disclosure of information, which seems to conflict with the principle of informed consent. For certain epidemiological studies non-disclosure is permissible, even essential, so as to not influence the spontaneous conduct under investigation, and to avoid obtaining responses that the respondent might give in order to please the questioner. Selective disclosure may be benign and ethically permissible, provided that it does not induce subjects to do what they would not otherwise consent to do. An ethical review committee may permit disclosure of only selected information when this course is justified.

Undue Influence

10. Prospective subjects may not feel free to refuse requests from those who have power or influence over them. Therefore the identity of the investigator or other person assigned to invite prospective subjects to participate must be made known to them. Investigators are expected to explain to the ethical review committee how they propose to neutralize such apparent influence. It is ethically questionable whether subjects should be recruited from among groups that are unduly influenced by persons in authority over them or by community leaders, if the study can be done with subjects who are not in this category.

Inducement to Participate

11. Individuals or communities should not be pressured to participate in a study. However, it can be hard to draw the line between exerting pressure or offering inappropriate inducements and creating legitimate motivation. The benefits of a study, such as increased or new knowledge, are proper inducements. However, when people or communities lack basic health services or money, the prospect of being rewarded by goods, services or cash payments can induce participation. To determine the ethical propriety of such inducements, they must be assessed in the light of the traditions of the culture.

12. Risks involved in participation should be acceptable to subjects even in the absence of inducement. It is acceptable to repay incurred expenses, such as for travel. Similarly, promises of compensation and care for damage, injury or loss of income should not be considered inducements.

Maximizing Benefit

Communication of Study Results

13. Part of the benefit that communities, groups and individuals may reasonably expect from participating in studies is that they will be told of findings that pertain to their health. Where findings could be applied in public health measures to improve community health, they should be communicated to the health authorities. In informing individuals of the findings and their pertinence to health, their level of literacy and comprehension must be considered. Research protocols should include provision for communicating such information to communities and individuals.

Research findings and advice to communities should be publicized by whatever suitable means are available. When HIV-prevalence studies are conducted by unlinked anonymous screening, there should be, where feasible, provision for voluntary HIV-antibody testing under conditions of informed consent, with pre- and post-test counseling, and assurance of confidentiality.

Impossibility of Communicating Study Results

14. Subjects of epidemiological studies should be advised that it may not be possible to inform them about findings that pertain to their health, but that they should not take this to mean that they are free of the disease or condition under study. Often it may not be possible to extract from pooled findings information pertaining to individuals and their families, but when findings indicate a need of health care, those concerned should be advised of means of obtaining personal diagnosis and advice.

When epidemiological data are unlinked, a disadvantage to subjects is that individuals at risk cannot be informed of useful findings pertinent to their health. When subjects cannot be advised individually to seek medical attention, the ethical duty to do good can be served by making pertinent health-care advice available to their communities.

Release of Study Results

15. Investigators may be unable to compel release of data held by governmental or commercial agencies, but as health professionals they have an ethical obligation to advocate the release of information that is in the public interest.

Sponsors of studies may press investigators to present their findings in ways that advance special interests, such as to show that a product or procedure is or is not harmful to health. Sponsors must not present interpretations or inferences, or theories and hypotheses, as if they were proven truths.

Healthcare for the Community Under Study

16. The undertaking of an epidemiological project in a developing country may create the expectation in the community concerned that it will be provided with health care, at least while the research workers are present. Such an expectation should not be frustrated, and, where people need health care, arrangements should be made to have them treated or they should be referred to a local health service that can provide the needed care.

Training Local Health Personnel

17. While studies are in progress, particularly in developing countries, the opportunity should be taken to train local health workers in skills and techniques that can be used to improve health services. For instance, by training them in the operation of measuring devices and calculating machines, when a study team departs it leaves something of value, such as the ability to monitor disease or mortality rates.

Minimizing Harm

Causing Harm and Doing Wrong

18. Investigators planning studies will recognize the risk of causing harm, in the sense of bringing disadvantage, and of doing wrong, in the sense of transgressing values. Harm may occur, for instance, when scarce health personnel are diverted from their routine duties to serve the needs of a study, or when, unknown to a community, its health-care priorities are changed. It is wrong to regard members of communities as only impersonal material for study, even if they are not harmed.

19. Ethical review must always assess the risk of subjects or groups suffering stigmatization, prejudice, loss of prestige or self-esteem, or economic loss as a result of taking part in a study. Investigators will inform ethical review committees and prospective subjects of perceived risks, and of proposals to prevent or mitigate them. Investigators must be able to demonstrate that the benefits outweigh the risks for both individuals and groups. There should be a thorough analysis to determine who would be at risk and who would benefit from the study. It is unethical to expose persons to avoidable risks disproportionate to the expected benefits, or to permit a known risk to remain if it can be avoided or at least minimized.

20. When a healthy person is a member of a population or sub-group at raised risk and engages in high-risk activities, it is unethical not to propose measures for protecting the population or sub-group.

Preventing Harm to Groups

21. Epidemiological studies may inadvertently expose groups as well as individuals to harm, such as economic loss, stigmatization, blame, or withdrawal of services. Investigators who find sensitive information that may put a group at risk of adverse criticism or treatment should be discreet in communicating and explaining their findings. When the location or circumstances of a study are important to understanding the results, the investigators will explain by what means they propose to protect the group from harm or disadvantage; such means include provisions for confidentiality and the use of language that does not imply moral criticism of subjects' behaviour.

Harmful Publicity

22. Conflict may appear between, on the one hand, doing no harm and, on the other, telling the truth and openly disclosing scientific findings. Harm may be mitigated by interpreting data in a way that protects the interests of those at risk, and is at the same time consistent with scientific integrity. Investigators should, where possible, anticipate and avoid misinterpretation that might cause harm.

Respect for Social Moeres

23. Disruption of social moeres is usually regarded as harmful. Although cultural values and social moeres must be respected, it may be a specific aim of an epidemiological study to stimulate change in certain customs or conventional behaviour to lead through change to healthful behaviour—for instance, with regard to diet or a hazardous occupation.

24. Although members of communities have a right not to have others impose an uninvited "good" on them, studies expected to result in health benefits are usually considered ethically acceptable and not harmful. Ethical review committees should consider a study's potential for beneficial change. However, investigators should not overstate such benefits, in case a community's agreement to participate is unduly influenced by its expectation of better health services.

Sensitivity to Different Cultures

25. Epidemiologists often investigate cultural groups other than their own, inside or outside their own countries, and undertake studies initiated from outside the culture, community or country in which the study is to be conducted. Sponsoring and host countries may differ in the ways in which, in their cultures, ethical values are understood and applied—for instance, with regard to autonomy of individuals.

Investigators must respect the ethical standards of their own countries and the cultural expectations of the societies in which epidemiological studies are undertaken, unless this implies a violation of a transcending moral rule. Investigators risk harming their reputation by pursuing work that host countries find acceptable but their own countries consider offensive. Similarly, they may transgress the cultural values of the host countries by uncritically conforming to the expectations of their own.

Confidentiality

26. Research may involve collecting and storing data relating to individuals and groups, and such data, if disclosed to third parties, may cause harm or distress. Consequently, investigators should make arrangements for pro-

protecting the confidentiality of such data by, for example, omitting information that might lead to the identification of individual subjects, or limiting access to the data, or by other means. It is customary in epidemiology to aggregate numbers so that individual identities are obscured. Where group confidentiality cannot be maintained or is violated, the investigators should take steps to maintain or restore a group's good name and status. Information obtained about subjects is generally divisible into:

Unlinked information, which cannot be linked, associated or connected with the person to whom it refers; as this person is not known to the investigator, confidentiality is not at stake and the question of consent does not arise.

Linked information, which may be:

- anonymous, when the information cannot be linked to the person to whom it refers except by a code or other means known only to that person, and the investigator cannot know the identity of the person;
- non-nominal, when the information can be linked to the person by a code (not including personal identification) known to the person and the investigator; or
- nominal or nominative, when the information is linked to the person by means of personal identification, usually the name.

Epidemiologists discard personal identifying information when consolidating data for purposes of statistical analysis. Identifiable personal data will not be used when a study can be done without personal identification—for instance, in testing unlinked anonymous blood samples for HIV infection. When personal identifiers remain on records used for a study, investigators should explain to review committees why this is necessary and how confidentiality will be protected. If, with the consent of individual subjects, investigators link different sets of data regarding individuals, they normally preserve confidentiality by aggregating individual data into tables or diagrams. In government service the obligation to protect confidentiality is frequently reinforced by the practice of swearing employees to secrecy.

Conflict of Interest

Identification of Conflict of Interest

27. It is an ethical rule that investigators should have no undisclosed conflict of interest with their study collaborators, sponsors or subjects. Investigators should disclose to the ethical review committee any potential conflict of interest. Conflict can arise when a commercial or other sponsor may wish to use study results to promote a product or service, or when it may not be politically convenient to disclose findings.

28. Epidemiological studies may be initiated, or financially or otherwise supported, by governmental or other agencies that employ investigators. In the occupational and environmental health fields, several well-defined special-interest groups may be in conflict: shareholders, management, labour, government regulatory agencies, public interest advocacy groups, and others. Epidemiological investigators may be employed by any of these groups. It can be difficult to avoid pressures resulting from such conflict of interest, and consequent distorted interpretations of study findings. Similar conflict may arise in studies of the effects of drugs and in testing medical devices.

29. Investigators and ethical review committees will be sensitive to the risk of conflict, and committees will not normally approve proposals in which conflict of interest is inherent. If, exceptionally, such a proposal is approved, the conflict of interest should be disclosed to prospective subjects and their communities.

30. There may appear to be conflict when subjects do not want to change their behaviour and investigators believe that they ought to do so for the sake of their health. However, this may not be a true conflict of interest, as the investigators are motivated by the subjects' health interests.

Scientific Objectivity and Advocacy

31. Honesty and impartiality are essential in designing and conducting studies, and presenting and interpreting findings. Data will not be withheld, misrepresented or manipulated. Investigators may discover health hazards that demand correction, and become advocates of means to protect and restore health. In this event, their advocacy must be seen to rely on objective, scientific data.

ETHICAL REVIEW PROCEDURES

Requirement of Ethical Review

32. The provisions for ethical review in a society are influenced by economic and political considerations, the organization of health care and research, and the degree of independence of investigators. Whatever the circumstances, there is a responsibility to ensure that the Declaration of Helsinki and the CIOMS International Guidelines for Biomedical Research Involving Human Subjects are taken into account in epidemiological studies.

33. The requirement that proposals for epidemiological studies be submitted to independent ethical review applies irrespective of the source of the proposals—academic, governmental, health-care, commercial, or other. Sponsors should recognize the necessity of ethical review and facilitate the establishment of ethical review committees. Sponsors and investigators are expected to submit their proposals to ethical review, and this should not be overlooked even when sponsors have legal power to permit investigators access to data. An exception is justified when epidemiologists must investigate outbreaks of acute communicable diseases. Then they must proceed without delay

to identify and control health risks. They cannot be expected to await the formal approval of an ethical review committee. Nevertheless, in such circumstances the investigator will, as far as possible, respect the rights of individuals, namely freedom, privacy, and confidentiality.

Ethical Review Committees

34. Ethical review committees may be created under the aegis of national or local health administrations, national medical research councils, or other nationally representative health-care bodies. The authority of committees operating on a local basis may be confined to one institution or extend to all biomedical studies undertaken in a defined political jurisdiction. However committees are created, and however their jurisdiction is defined, they should establish working rules—regarding, for instance, frequency of meetings, a quorum of members, decision-making procedures, and review of decisions, and they should issue such rules to prospective investigators.

35. In a highly centralized administration, a national review committee may be constituted to review study protocols from both scientific and ethical standpoints. In countries with a decentralized administration, protocols are more effectively and conveniently reviewed at a local or regional level. Local ethical review committees have two responsibilities:

- to verify that all proposed interventions have been assessed for safety by a competent expert body, and
- to ensure that all other ethical issues are satisfactorily resolved.

36. Local review committees act as a panel of investigators' peers, and their composition should be such as can ensure adequate review of the study proposals referred to them. Their membership should include epidemiologists, other health practitioners, and lay persons qualified to represent a range of community, cultural and moral values. Committees should have diverse composition and include representatives of any populations specially targeted for study. The members should change periodically to prevent individuals from becoming unduly influential, and to widen the network involved in ethical review. Independence from the investigators is maintained by precluding any member with a direct interest in a proposal from participating in its assessment.

Ethical Conduct of Members of Review Committees

37. Ethical review committee members must carefully guard against any tendencies to unethical conduct on their own part. In particular, they should protect the confidentiality of review-committee documents and discussions. Also, they should not compel investigators to submit to unnecessary repetition of review.

Representation of the Community

38. The community to be studied should be represented in the ethical review process. This is consistent with respect for the culture, the dignity and self-reliance of the community, and the aim of achieving community members' full understanding of the study. It should not be considered that lack of formal education disqualifies community members from joining in constructive discussion on issues relating to the study and the application of its findings.

Balancing Personal and Social Perspectives

39. In performing reviews, committees will consider both personal and social perspectives. While, at the personal level, it is essential to ensure individual informed and free consent, such consent alone may not be sufficient to render a study ethical if the individual's community finds the study objectionable. Social values may raise broad issues that affect future populations and the physical environment. For example, in proposals for the widespread application of measures to control intermediate hosts of disease organisms, investigators will anticipate the effects of those measures on communities and the environment, and review committees will ensure that there is adequate provision for the investigators to monitor the application of the measures so as to prevent unwanted effects.

Assuring Scientific Soundness

40. The primary functions of ethical review are to protect human subjects against risks of harm or wrong, and to facilitate beneficial studies. Scientific review and ethical review cannot be considered separately: a study that is scientifically unsound is unethical in exposing subjects to risk or inconvenience and achieving no benefit in knowledge. Normally, therefore, ethical review committees consider both scientific and ethical aspects. An ethical review committee may refer technical aspects of scientific review to a scientifically qualified person or committee, but will reach its own decision, based on such qualified advice, on scientific soundness. If a review committee is satisfied that a proposal is scientifically sound, it will then consider whether any risk to the subject is justified by the expected benefit, and whether the proposal is satisfactory with regard to informed consent and other ethical requirements.

Assessment of Safety and Quality

41. All drugs and devices under investigation must meet adequate standards of safety. In this respect, many countries lack resources to undertake independent assessment of technical data. A governmental multidisciplinary committee with authority to co-opt experts is the most suitable body for assessing the safety and quality of medicines, devices and procedures. Such a committee should include clinicians, pharmacologists, statisticians and epidemiologists, among others; for epidemiological studies, epidemiologists occupy a position of obvious significance. Ethical review procedures should provide for consultation with such a committee.

Equity in the Selection of Subjects

42. Epidemiological studies are intended to benefit populations, but individual subjects are expected to accept any risks associated with studies. When research is intended to benefit mostly the better off or healthier members of

a population, it is particularly important in selecting subjects to avoid inequity on the basis of age, socioeconomic status, disability or other variables. Potential benefits and harm should be distributed equitably within and among communities that differ on grounds of age, gender, race, or culture, or other variables.

Vulnerable and Dependent Groups

43. Ethical review committees should be particularly vigilant in the case of proposals involving populations primarily of children, pregnant and nursing women, persons with mental illness or handicap, members of communities unfamiliar with medical concepts, and persons with restricted freedom to make truly independent choices, such as prisoners and medical students. Similar vigilance is called for in the case of proposals for invasive research with no direct benefit to its subjects.

Control Groups

44. Epidemiological studies that require control (comparison) or placebo treated (ie, non-treated) groups are governed by the same ethical standards as those that apply to clinical trials. Important principles are that:

- (i) the control group in a study of a condition that can cause death, disability or serious distress should receive the most appropriate currently established therapy; and
- (ii) if a procedure being tested against controls is demonstrated to be superior, it should be offered promptly to members of the control group.

A study will be terminated prematurely if the outcome in one group is clearly superior to that in the other, and all subjects will be offered the better treatment. Research protocols should include “stopping rules,” ie, procedures to monitor for, and act upon, such an event. Investigators must continually bear in mind the potential benefits of the study to the control group, and the prospect of improved health care from applying the findings to the control group.

Randomization

45. Trials in which the choice of regimen or procedure is determined by random allocation should be conducted only when there is genuine uncertainty about differences in outcome of two or more regimens or procedures. Where randomization is to be used, all subjects will be informed of the uncertainty about optimum regimens or procedures, and that the reason for the trial is to determine which of two or more is in the subjects’ best interests. Informing subjects about such uncertainty can in itself arouse anxiety among patients, who may already be anxious for other reasons; therefore, tact and delicacy are required in communicating the information. Ethical review committees should ascertain whether investigators refer explicitly to informing subjects about this uncertainty, and should enquire what will be done to allay subjects’ anxiety about it.

Random allocation also can cause anxiety: persons chosen for, or excluded from, the experimental regimen or procedure may become anxious or concerned about the reasons for their being chosen or excluded. Investigators may have to communicate to members of the study population some basic concepts about application of the laws of chance, and reassure them that the process of random allocation is not discriminatory.

Provision for Multi-centre Studies

46. When participation in a multi-centre study is proposed according to a common protocol, a committee will respect different opinions of other committees, while not compromising on the application of the ethical standards that it expects investigators to observe; and it will attempt to reconcile differences so as to preserve the benefits that only a multi-centre study can achieve. One way of doing so could be to include in the common protocol the necessary procedures. Another would be for the several committees to delegate their review functions to a joint committee of the centres collaborating in the study.

Compensation for Accidental Injury

47. Some epidemiological studies may inadvertently cause harm. Monetary losses should be promptly repaid. Compensation is difficult when it is not appropriate to make monetary payments. Breach of confidentiality or insensitive publication of study findings, leading to loss of group prestige, or to indignity, may be difficult to remedy. When harm results from a study, the body that has sponsored or endorsed the study should be prepared to make good the injury, by public apology or reparation.

Externally Sponsored Studies

48. Externally sponsored studies are studies undertaken in a host country but initiated, financed, and sometimes wholly or partly carried out by an external international or national agency, with the collaboration or agreement of the authorities or the host country.

Such a study implies two ethical obligations:

- The initiating agency should submit the study protocol to ethical review, in which the ethical standards should be no less exacting than they would be for a study carried out in the initiating country.
- The ethical review committee in the host country should satisfy itself that the proposed study meets its own ethical requirements.

49. It is in the interest of the host country to require that proposals initiated and financed externally be submitted for ethical approval in the initiating country, and for endorsement by a responsible authority of the same country, such as a health administration, a research council, or an academy of medicine or science.

50. A secondary objective of externally sponsored studies should be the training of health personnel of the host country to carry out similar study projects independently.

51. Investigators must comply with the ethical rules of the funding country and the host country. Therefore, they must be prepared to submit study proposals to ethical review committees in each country. Alternatively, there may be agreement to the decision of a single or joint ethical review committee. Moreover, if an international agency sponsors a study, its own ethical review requirements may have to be satisfied.

Distinguishing Between Research and Programme Evaluation

52. It may at times be difficult to decide whether a particular proposal is for an epidemiological study or for evaluation of a programme on the part of a health-care institution or department. The defining attribute of research is that it is designed to produce new, generalizable knowledge, as distinct from knowledge pertaining only to a particular individual or programme.

For instance, a governmental or hospital department may want to examine patients' records to determine the safety and efficacy of a facility, unit or procedure. If the examination is for research purposes, the proposal should be submitted to the committee that considers the ethical features of research proposals. However, if it is for the purpose of programme evaluation, conducted perhaps by staff of the institution to evaluate a therapeutic programme for its effects, the proposal may not need to be submitted to ethical review; on the contrary, it could be considered poor practice and unethical not to undertake this type of quality assurance. The prospect of benefit or avoidance of harm to patients may constitute an ethical value that outweighs the risk of breaching the confidentiality of former patients whose medical records are liable to be inspected without their consent.

If it is not clear whether a proposal involves epidemiological study or routine practice, it should be submitted to the ethical review committee responsible for epidemiological protocols, for its opinion on whether the proposal falls within its mandate.

Information to Be Provided by Investigators

53. Whatever the pattern of the procedure of ethical review, the investigator must submit a detailed protocol comprising:

- a clear statement of the objectives, having regard to the present state of knowledge, and a justification for undertaking the investigation in human subjects;
- a precise description of all proposed procedures and interventions, including intended dosages of drugs and planned duration of treatment;
- a statistical plan indicating the number of subjects to be involved;
- the criteria for terminating the study; and
- the criteria determining admission and withdrawal of individual subjects, including full details of the procedure for obtaining informed consent.

Also, the protocol should:

- include information to establish the safety of each proposed procedure and intervention, and of any drug, vaccine or device to be tested, including the results of relevant laboratory and animal research;
- specify the presumed benefits to subjects, and the possible risks of proposed procedures;
- indicate the means and documents proposed to be used for eliciting informed consent, or, when such consent cannot be requested, state what approved alternative means of obtaining agreement will be used, and how it is proposed to protect the rights and assure the welfare of subjects;
- provide evidence that the investigator is properly qualified and experienced, or, when necessary, works under a competent supervisor, and that the investigator has access to adequate facilities for the safe and efficient conduct of the research;
- describe the proposed means of protecting confidentiality during the processing and publication of study results; and
- refer to any other ethical considerations that may be involved, and indicate that the provisions of the Declaration of Helsinki will be respected.

Available at: <http://www.cdc.gov/od/ads/intlgui3.htm>. Accessed 23 April 2002; formatted to *Textbooks of Military Medicine* style.

CHAPTER 19: ATTACHMENT 3

CODE OF FEDERAL REGULATIONS, TITLE 32—NATIONAL DEFENSE

CHAPTER I—OFFICE OF THE SECRETARY OF DEFENSE

PART 219—PROTECTION OF HUMAN SUBJECTS

Table of Contents

Sec. 219.101	To what does this policy apply?
Sec. 219.102	Definitions.
Sec. 219.103	Assuring compliance with this policy—research conducted or supported by any Federal Department or Agency.
Sec. 219.107	IRB membership.
Sec. 219.108	IRB functions and operations.
Sec. 219.109	IRB review of research.
Sec. 219.110	Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.
Sec. 219.111	Criteria for IRB approval of research.
Sec. 219.112	Review by institution.
Sec. 219.113	Suspension or termination of IRB approval of research.
Sec. 219.114	Cooperative research.
Sec. 219.115	IRB records.
Sec. 219.116	General requirements for informed consent.
Sec. 219.117	Documentation of informed consent.
Sec. 219.118	Applications and proposals lacking definite plans for involvement of human subjects.
Sec. 219.119	Research undertaken without the intention of involving human subjects.
Sec. 219.120	Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal Department or Agency.
Sec. 219.122	Use of Federal funds.
Sec. 219.123	Early termination of research support: Evaluation of applications and proposals.
Sec. 219.124	Conditions.

Sec. 219.101 To what does this policy apply?

- (a) Except as provided in paragraph (b) of this section, this policy applies to all research involving human subjects conducted, supported or otherwise subject to regulation by any federal department or agency which takes appropriate administrative action to make the policy applicable to such research. This includes research conducted by federal civilian employees or military personnel, except that each department or agency head may adopt such procedural modifications as may be appropriate from an administrative standpoint. It also includes research conducted, supported, or otherwise subject to regulation by the federal government outside the United States.
 - (1) Research that is conducted or supported by a federal department or agency, whether or not it is regulated as defined in Sec. 219.102(e), must comply with all sections of this policy.
 - (2) Research that is neither conducted nor supported by a federal department or agency but is subject to regulation as defined in Sec. 219.102(e) must be reviewed and approved, in compliance with Sec. 219.101, Sec. 219.102, and Sec. 219.107 through Sec. 219.117 of this policy, by an institutional review board (IRB) that operates in accordance with the pertinent requirements of this policy.
- (b) Unless otherwise required by department or agency heads, research activities in which the only involvement of human subjects will be in one or more of the following categories are exempt from this policy:

- (1) Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.
- (2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:
 - (i) Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and
 - (ii) Any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.
- (3) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (b)(2) of this section, if:
 - (i) The human subjects are elected or appointed public officials or candidates for public office; or
 - (ii) Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.
- (4) Research, involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.
- (5) Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine:
 - (i) Public benefit or service programs;
 - (ii) Procedures for obtaining benefits or services under those programs;
 - (iii) Possible changes in or alternatives to those programs or procedures; or
 - (iv) Possible changes in methods or levels of payment for benefits or services under those programs.
- (6) Taste and food quality evaluation and consumer acceptance studies,
 - (i) If wholesome foods without additives are consumed or
 - (ii) If a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.
- (c) Department or agency heads retain final judgment as to whether a particular activity is covered by this policy.
- (d) Department or agency heads may require that specific research activities or classes of research activities conducted, supported, or otherwise subject to regulation by the department or agency but not otherwise covered by this policy, comply with some or all of the requirements of this policy.
- (e) Compliance with this policy requires compliance with pertinent federal laws or regulations which provide additional protections for human subjects.
- (f) This policy does not affect any state or local laws or regulations which may otherwise be applicable and which provide additional protections for human subjects.
- (g) This policy does not affect any foreign laws or regulations which may otherwise be applicable and which provide additional protections to human subjects of research.
- (h) When research covered by this policy takes place in foreign countries, procedures normally followed in the foreign countries to protect human subjects may differ from those set forth in this policy. (An example is a foreign institution which complies with guidelines consistent with the World Medical Assembly Declaration (Declaration of Helsinki amended 1989) issued either by sovereign states or by an organization whose function for the protection of human research subjects is internationally recognized.) In these circumstances, if a department or agency head determines that the procedures prescribed by the institution afford protections that are at least equivalent to those provided in this policy, the department or agency head may approve the substitution of the foreign procedures in lieu of the procedural requirements provided in this policy. Except when otherwise required by statute, Executive Order, or the department or agency head, notices of these actions as they occur will be published in the Federal Register or will be otherwise published as provided in department or agency procedures.¹

- (i) Unless otherwise required by law, department or agency heads may waive the applicability of some or all of the provisions of this policy to specific research activities or classes of research activities otherwise covered by this policy. Except when otherwise required by statute or Executive Order, the department or agency head shall forward advance notices of these actions to the Office for Protection from Research Risks, Department of Health and Human Services (HHS), and shall also publish them in the Federal Register or in such other manner as provided in department or agency procedures.²

Sec. 219.102 Definitions.

- (a) Department or agency head means the head of any federal department or agency and any other officer or employee of any department or agency to whom authority has been delegated.
- (b) Institution means any public or private entity or agency (including federal, state, and other agencies).
- (c) Legally authorized representative means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.
- (d) Research means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.
- (e) Research subject to regulation, and similar terms are intended to encompass those research activities for which a federal department or agency has specific responsibility for regulating as a research activity, (for example, Investigational New Drug requirements administered by the Food and Drug Administration). It does not include research activities which are incidentally regulated by a federal department or agency solely as part of the department's or agency's broader responsibility to regulate certain types of activities whether research or non-research in nature (for example, Wage and Hour requirements administered by the Department of Labor).
- (f) Human subject means a living individual about whom an investigator (whether professional or student) conducting research obtains
 - (1) Data through intervention or interaction with the individual, or
 - (2) Identifiable private information.Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. Interaction includes communication or interpersonal contact between investigator and subject. "Private information" includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (ie, the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.
- (g) IRB means an institutional review board established in accord with and for the purposes expressed in this policy.
- (h) IRB approval means the determination of the IRB that the research has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and federal requirements.
- (i) Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.
- (j) Certification means the official notification by the institution to the supporting department or agency, in accordance with the requirements of this policy, that a research project or activity involving human subjects has been reviewed and approved by an IRB in accordance with an approved assurance.

Sec. 219.103 Assuring compliance with this policy—research conducted or supported by any Federal Department or Agency.

- (a) Each institution engaged in research which is covered by this policy and which is conducted or supported by a federal department or agency shall provide written assurance satisfactory to the department or agency head that it will comply with the requirements set forth in this policy. In lieu of requiring submission of an assurance, individual department or agency heads shall accept the existence of a current assurance, appropriate for the research in question, on file with the Office for Protection from Research Risks, HHS, and approved for federalwide use by that office. When the existence of an HHS-approved assurance is accepted in lieu of requiring submission of an assurance, reports (except certification) required by this policy to be made to department and agency heads shall also be made to the Office for Protection from Research Risks, HHS.
- (b) Departments and agencies will conduct or support research covered by this policy only if the institution has an assurance approved as provided in this section, and only if the institution has certified to the department or agency head that the research has been reviewed and approved by an IRB provided for in the assurance, and will be subject to continuing review by the IRB. Assurances applicable to federally supported or conducted research shall at a minimum include:
 - (1) A statement of principles governing the institution in the discharge of its responsibilities for protecting the rights and welfare of human subjects of research conducted at or sponsored by the institution, regardless of whether the research is subject to federal regulation. This may include an appropriate existing code, declaration, or statement of ethical principles, or a statement formulated by the institution itself. This requirement does not preempt provisions of this policy applicable to department- or agency-supported or regulated research and need not be applicable to any research exempted or waived under Sec. 219.101 (b) or (i).
 - (2) Designation of one or more IRBs established in accordance with the requirements of this policy, and for which provisions are made for meeting space and sufficient staff to support the IRB's review and recordkeeping duties.
 - (3) A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution; for example: full-time employee, part-time employee, member of governing panel or board, stockholder, paid or unpaid consultant. Changes in IRB membership shall be reported to the department or agency head, unless in accord with Sec. 219.103(a) of this policy, the existence of an HHS-approved assurance is accepted. In this case, change in IRB membership shall be reported to the Office for Protection from Research Risks, HHS.
 - (4) Written procedures which the IRB will follow (i) for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; (ii) for determining which projects require review more often than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review; and (iii) for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.
 - (5) Written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the department or agency head of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB and (ii) any suspension or termination of IRB approval.
- (c) The assurance shall be executed by an individual authorized to act for the institution and to assume on behalf of the institution the obligations imposed by this policy and shall be filed in such form and manner as the department or agency head prescribes.
- (d) The department or agency head will evaluate all assurances submitted in accordance with this policy through such officers and employees of the department or agency and such experts or consultants engaged for this purpose as the department or agency head determines to be appropriate. The department or agency head's evaluation will take into consideration the adequacy of the proposed IRB in light of the anticipated scope of the institution's research activities and the types of subject populations likely to be involved, the appropriateness of the proposed initial and continuing review procedures in light of the probable risks, and the size and complexity of the institution.

- (e) On the basis of this evaluation, the department or agency head may approve or disapprove the assurance, or enter into negotiations to develop an approvable one. The department or agency head may limit the period during which any particular approved assurance or class of approved assurances shall remain effective or otherwise condition or restrict approval.
- (f) Certification is required when the research is supported by a federal department or agency and not otherwise exempted or waived under Sec. 219.101 (b) or (i). An institution with an approved assurance shall certify that each application or proposal for research covered by the assurance and by Sec. 219.103 of this Policy has been reviewed and approved by the IRB. Such certification must be submitted with the application or proposal or by such later date as may be prescribed by the department or agency to which the application or proposal is submitted. Under no condition shall research covered by Sec. 219.103 of the Policy be supported prior to receipt of the certification that the research has been reviewed and approved by the IRB. Institutions without an approved assurance covering the research shall certify within 30 days after receipt of a request for such a certification from the department or agency, that the application or proposal has been approved by the IRB. If the certification is not submitted within these time limits, the application or proposal may be returned to the institution.

(Approved by the Office of Management and Budget under control number 9999-0020)

[56 FR 28012, 28021, June 18, 1991, as amended at 56 FR 29756, June 28, 1991]

Sec 219.104–219.106 Reserved

Sec. 219.107 IRB membership.

- (a) Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects.
- (b) Every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender. No IRB may consist entirely of members of one profession.
- (c) Each IRB shall include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas.
- (d) Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.
- (e) No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.
- (f) An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

Sec. 219.108 IRB functions and operations.

In order to fulfill the requirements of this policy each IRB shall:

- (a) Follow written procedures in the same detail as described in Sec. 219.103(b)(4) and, to the extent required by, Sec. 219.103(b)(5).
- (b) Except when an expedited review procedure is used (see Sec. 219.110), review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. In order for the research to be approved, it shall receive the approval of a majority of those members present at the meeting.

Sec. 219.109 IRB review of research.

- (a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by this policy.
- (b) An IRB shall require that information given to subjects as part of informed consent is in accordance with Sec. 219.116. The IRB may require that information, in addition to that specifically mentioned in Sec. 219.116, be given to the subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects.
- (c) An IRB shall require documentation of informed consent or may waive documentation in accordance with Sec. 219.117.
- (d) An IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing.
- (e) An IRB shall conduct continuing review of research covered by this policy at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research.

(Approved by the Office of Management and Budget under control number 9999-0020)

Sec. 219.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.

- (a) The Secretary, HHS, has established, and published as a Notice in the Federal Register, a list of categories of research that may be reviewed by the IRB through an expedited review procedure. The list will be amended, as appropriate after consultation with other departments and agencies, through periodic republication by the Secretary, HHS, in the Federal Register. A copy of the list is available from the Office for Protection from Research Risks, National Institutes of Health, HHS, Bethesda, Maryland 20892.
- (b) An IRB may use the expedited review procedure to review either or both of the following:
 - (1) Some or all of the research appearing on the list and found by the reviewer(s) to involve no more than minimal risk,
 - (2) Minor changes in previously approved research during the period (of one year or less) for which approval is authorized.

Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the non-expedited procedure set forth in Sec. 219.108(b).
- (c) Each IRB which uses an expedited review procedure shall adopt a method for keeping all members advised of research proposals which have been approved under the procedure.
- (d) The department or agency head may restrict, suspend, terminate, or choose not to authorize an institution's or IRB's use of the expedited review procedure.

Sec. 219.111 Criteria for IRB approval of research.

- (a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied:
 - (1) Risks to subjects are minimized:
 - (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and
 - (ii) Whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
 - (2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research

(for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

- (3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.
 - (4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by Sec. 219.116.
 - (5) Informed consent will be appropriately documented, in accordance with, and to the extent required by Sec. 219.117.
 - (6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
 - (7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.
- (b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

Sec. 219.112 Review by institution.

Research covered by this policy that has been approved by an IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. However, those officials may not approve the research if it has not been approved by an IRB.

Sec. 219.113 Suspension or termination of IRB approval of research.

An IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator, appropriate institutional officials, and the department or agency head.

(Approved by the Office of Management and Budget under control number 9999-0020)

Sec. 219.114 Cooperative research.

Cooperative research projects are those projects covered by this policy which involve more than one institution. In the conduct of cooperative research projects, each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with this policy. With the approval of the department or agency head, an institution participating in a cooperative project may enter into a joint review arrangement, rely upon the review of another qualified IRB, or make similar arrangements for avoiding duplication of effort.

Sec. 219.115 IRB records.

- (a) An institution, or when appropriate an IRB, shall prepare and maintain adequate documentation of IRB activities, including the following:
 - (1) Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects.
 - (2) Minutes of IRB meetings which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution.
 - (3) Records of continuing review activities.
 - (4) Copies of all correspondence between the IRB and the investigators.
 - (5) A list of IRB members in the same detail as described in Sec. 219.103(b)(3).
 - (6) Written procedures for the IRB in the same detail as described in Sec. 219.103(b)(4) and Sec. 219.103(b)(5).
 - (7) Statements of significant new findings provided to subjects, as required by Sec. 219.116(b)(5).

- (b) The records required by this policy shall be retained for at least 3 years, and records relating to research which is conducted shall be retained for at least 3 years after completion of the research. All records shall be accessible for inspection and copying by authorized representatives of the department or agency at reasonable times and in a reasonable manner.

(Approved by the Office of Management and Budget under control number 9999-0020)

Sec. 219.116 General requirements for informed consent.

Except as provided elsewhere in this policy, no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

- (a) Basic elements of informed consent. Except as provided in paragraph (c) or (d) of this section, in seeking informed consent the following information shall be provided to each subject:
 - (1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;
 - (2) A description of any reasonably foreseeable risks or discomforts to the subject;
 - (3) A description of any benefits to the subject or to others which may reasonably be expected from the research;
 - (4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
 - (5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;
 - (6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;
 - (7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and
 - (8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
- (b) Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:
 - (1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;
 - (2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;
 - (3) Any additional costs to the subject that may result from participation in the research;
 - (4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;
 - (5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; and
 - (6) The approximate number of subjects involved in the study.
- (c) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth above, or waive the requirement to obtain informed consent provided the IRB finds and documents that:
 - (1) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine:

- (i) Public benefit of service programs;
 - (ii) Procedures for obtaining benefits or services under those programs;
 - (iii) Possible changes in or alternatives to those programs or procedures; or
 - (iv) Possible changes in methods or levels of payment for benefits or services under those programs; and
 - (2) The research could not practicably be carried out without the waiver or alteration.
 - (d) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:
 - (1) The research involves no more than minimal risk to the subjects;
 - (2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;
 - (3) The research could not practicably be carried out without the waiver or alteration; and
 - (4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.
 - (e) The informed consent requirements in this policy are not intended to preempt any applicable federal, state, or local laws which require additional information to be disclosed in order for informed consent to be legally effective.
 - (f) Nothing in this policy is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable federal, state, or local law.
- (Approved by the Office of Management and Budget under control number 9999-0020)

Sec. 219.117 Documentation of informed consent.

- (a) Except as provided in paragraph (c) of this section, informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form.
- (b) Except as provided in paragraph (c) of this section, the consent form may be either of the following:
 - (1) A written consent document that embodies the elements of informed consent required by Sec. 219.116. This form may be read to the subject or the subject's legally authorized representative, but in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed; or
 - (2) A short form written consent document stating that the elements of informed consent required by Sec. 219.116 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative, in addition to a copy of the short form.
- (c) An IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds either:
 - (1) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or
 - (2) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

In cases in which the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research.

(Approved by the Office of Management and Budget under control number 9999-0020)

Sec. 219.118 Applications and proposals lacking definite plans for involvement of human subjects.

Certain types of applications for grants, cooperative agreements, or contracts are submitted to departments or agencies with the knowledge that subjects may be involved within the period of support, but definite plans would not normally be set forth in the application or proposal. These include activities such as institutional type grants when selection of specific projects is the institution's responsibility; research training grants in which the activities involv-

ing subjects remain to be selected; and projects in which human subjects' involvement will depend upon completion of instruments, prior animal studies, or purification of compounds. These applications need not be reviewed by an IRB before an award may be made. However, except for research exempted or waived under Sec. 219.101 (b) or (i), no human subjects may be involved in any project supported by these awards until the project has been reviewed and approved by the IRB, as provided in this policy, and certification submitted, by the institution, to the department or agency.

Sec. 219.119 Research undertaken without the intention of involving human subjects.

In the event research is undertaken without the intention of involving human subjects, but it is later proposed to involve human subjects in the research, the research shall first be reviewed and approved by an IRB, as provided in this policy, a certification submitted, by the institution, to the department or agency, and final approval given to the proposed change by the department or agency.

Sec. 219.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal Department or Agency.

- (a) The department or agency head will evaluate all applications and proposals involving human subjects submitted to the department or agency through such officers and employees of the department or agency and such experts and consultants as the department or agency head determines to be appropriate. This evaluation will take into consideration the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained.
- (b) On the basis of this evaluation, the department or agency head may approve or disapprove the application or proposal, or enter into negotiations to develop an approvable one.

Sec 219.121 Reserved

Sec. 219.122 Use of Federal funds.

Federal funds administered by a department or agency may not be expended for research involving human subjects unless the requirements of this policy have been satisfied.

Sec. 219.123 Early termination of research support: Evaluation of applications and proposals.

- (a) The department or agency head may require that department or agency support for any project be terminated or suspended in the manner prescribed in applicable program requirements, when the department or agency head finds an institution has materially failed to comply with the terms of this policy.
- (b) In making decisions about supporting or approving applications or proposals covered by this policy the department or agency head may take into account, in addition to all other eligibility requirements and program criteria, factors such as whether the applicant has been subject to a termination or suspension under paragraph (a) of this section and whether the applicant or the person or persons who would direct or has have directed the scientific and technical aspects of an activity has have, in the judgment of the department or agency head, materially failed to discharge responsibility for the protection of the rights and welfare of human subjects (whether or not the research was subject to federal regulation).

Sec. 219.124 Conditions.

With respect to any research project or any class of research projects the department or agency head may impose additional conditions prior to or at the time of approval when in the judgment of the department or agency head additional conditions are necessary for the protection of human subjects.

Endnotes:

1. [56 FR 28012, 28021, June 18, 1991, as amended at 56 FR 29756, June 28, 1991.]
2. Institutions with HHS-approved assurances on file will abide by provisions of title 45 CFR part 46 subparts A-D. Some of the other Departments and Agencies have incorporated all provisions of title 45 CFR part 46 into their policies and procedures as well. However, the exemptions at 45 CFR 46.101(b) do not apply to research involving prisoners, fetuses, pregnant women, or human in vitro fertilization, subparts B and C. The exemption at 45 CFR 46.101(b)(2), for research involving survey or interview procedures or observation of public behavior, does not apply to research with children, subpart D, except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

Available at: <http://www.he.afrl.af.mil/humansubject/32cfr219.html>. Accessed 22 April 2002; formatted to *Textbooks of Military Medicine* style.

CHAPTER 19: ATTACHMENT 4

INTERNATIONAL ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

Council for International Organizations of Medical Sciences (CIOMS)

The Council for International Organizations of Medical Sciences (CIOMS) announces the publication of its revised/updated International Ethical Guidelines for Biomedical Research Involving Human Subjects. This 2002 text supersedes the 1993 Guidelines. It is the third in the series of biomedical-research ethical guidelines issued by CIOMS since 1982. Its core consists of 21 guidelines with commentaries. A prefatory section outlines the historical background and the revision process, and includes an introduction, an account of earlier instruments and guidelines, a statement of ethical principles and a preamble. An Appendix lists the items to be included in the research protocol to be submitted for scientific and ethical review and clearance. Appendices include also the World Medical Association's Declaration of Helsinki. The Guidelines relate mainly to ethical justification and scientific validity of research; ethical review; informed consent; vulnerability of individuals, groups, communities and populations; women as research subjects; equity regarding burdens and benefits; choice of control in clinical trials; confidentiality; compensation for injury; strengthening of national or local capacity for ethical review; and obligations of sponsors to provide health-care services. Their scope reflects the changes, the advances and the controversies that have characterized biomedical research ethics in the last two decades. Like those of 1982 and 1993, the 2002 CIOMS Guidelines are designed to be of use to countries in defining national policies on the ethics of biomedical research involving human subjects, applying ethical standards in local circumstances, and establishing or improving ethical review mechanisms. A particular aim is to reflect the conditions and the needs of low-resource countries, and the implications for multinational or transnational research in which they may be partners. [ISBN 92 9036 075 5; Price: Swiss francs 20; Order from CIOMS, c/o WHO, Avenue Appia 20, CH 1211 Geneva 27, Switzerland. E-mail: cioms@who.int; Tel. (+41 22) 791 34 13, Fax: (+41 22) 791 31 11] International Ethical Guidelines for Biomedical Research Involving Human Subjects, Prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO).

CIOMS
Geneva
2002

CONTENTS

ACKNOWLEDGEMENTS

BACKGROUND

INTRODUCTION

INTERNATIONAL INSTRUMENTS AND GUIDELINES

GENERAL ETHICAL PRINCIPLES

PREAMBLE

THE GUIDELINES

- Guideline 1: Ethical justification and scientific validity of biomedical research involving human subjects**
- Guideline 2: Ethical review committees**
- Guideline 3: Ethical review of externally sponsored research**
- Guideline 4: Individual informed consent**
- Guideline 5: Obtaining informed consent: Essential information for prospective research subjects**
- Guideline 6: Obtaining informed consent: Obligations of sponsors and investigators**
- Guideline 7: Inducement to participate**
- Guideline 8: Benefits and risks of study participation**
- Guideline 9: Special limitations on risk when research involves individuals who are not capable of giving informed consent**
- Guideline 10: Research in populations and communities with limited resources**
- Guideline 11: Choice of control in clinical trials**
- Guideline 12: Equitable distribution of burdens and benefits in the selection of groups of subjects in research**
- Guideline 13: Research involving vulnerable persons**
- Guideline 14: Research involving children**

- Guideline 15:** Research involving individuals who by reason of mental or behavioural disorders are not capable of giving adequately informed consent
 - Guideline 16:** Women as research participants
 - Guideline 17:** Pregnant women as research participants
 - Guideline 18:** Safeguarding confidentiality
 - Guideline 19:** Right of injured subjects to treatment and compensation
 - Guideline 20:** Strengthening capacity for ethical and scientific review and biomedical research
 - Guideline 21:** Ethical obligation of external sponsors to provide health-care services
- Appendix 1: Items to be included in a protocol (or associated documents) for biomedical research involving human subjects.
- Appendix 2: The Declaration of Helsinki
- Appendix 3: The phases of clinical trials of vaccines and drugs

ACKNOWLEDGEMENTS

The Council for International Organizations of Medical Sciences (CIOMS) acknowledges the substantial financial contribution of the Joint United Nations Programme on HIV / AIDS (UNAIDS) to the preparation of the 2002 International Ethical Guidelines for Biomedical Research Involving Human Subjects. The World Health Organization in Geneva contributed generously also through the departments of Reproductive Health and Research, Essential Drugs and Medicines Policy, Vaccines and Biologicals, and HIV / AIDS / Sexually Transmitted Infections, as well as the Special Programme for Research and Training in Tropical Diseases. CIOMS was at all times free to avail of the services and facilities of WHO. CIOMS acknowledges also with much appreciation the financial support to the project from the Government of Finland, the Government of Switzerland, the Swiss Academy of Medical Sciences, the Fogarty International Center at the National Institutes of Health, USA, and the Medical Research Council of the United Kingdom. A number of institutions and organizations made valuable contributions by making their experts available at no cost to CIOMS for the three meetings held in relation to the revision project. This has been highly appreciated. The task of finalizing the various drafts was in the hands of Professor Robert J. Levine, who served as consultant to the project and chair of the steering committee, and whose profound knowledge and understanding of the field is remarkable. He was ably assisted by Dr James Gallagher of the CIOMS secretariat, who managed the electronic discussion and endeavoured to accommodate or reflect in the text the numerous comments received. He also edited the final text. Special mention must be made of the informal drafting group set up to bring the influence of various cultures to bear on the process. The group, with two members of the CIOMS secretariat, met for five days in New York in January 2001 and continued for several months to interact electronically with one another and with the secretariat to prepare the third draft, posted on the CIOMS website in June 2001: Fernando Lolas Stepke (chair), John Bryant, Leonardo de Castro, Robert Levine, Ruth Macklin, and Godfrey Tangwa; the group continued from October 2001, together with Florencia Luna and Rodolfo Saracci, to cooperate in preparing the fourth draft. The contribution of this group was invaluable. The interest and comments of the many organizations and individuals who responded to the several drafts of the guidelines posted on the CIOMS website or otherwise made available are gratefully acknowledged (Appendix 6) At CIOMS, Sev Fluss was at all times ready and resourceful when consulted, with advice and constructive comment, and Mrs Kathryn Chalaby-Amsler responded most competently to the sometimes considerable demands made on her administrative and secretarial skills.

BACKGROUND

The Council for International Organizations of Medical Sciences (CIOMS) is an international nongovernmental organization in official relations with the World Health Organization (WHO). It was founded under the auspices of WHO and the United Nations Educational, Scientific and Cultural Organization (UNESCO) in 1949 with among its mandates that of maintaining collaborative relations with the United Nations and its specialized agencies, particularly with UNESCO and WHO.

CIOMS, in association with WHO, undertook its work on ethics in relation to biomedical research in the late 1970s. At that time, newly independent WHO Member States were setting up health-care systems. WHO was not then in a position to promote ethics as an aspect of health care or research. It was thus that CIOMS set out, in cooperation with WHO, to prepare guidelines "to indicate how the ethical principles that should guide the conduct of biomedical research involving human subjects, as set forth in the Declaration of Helsinki, could be effectively applied, particularly in developing countries, given their socioeconomic circumstances, laws and regulations, and executive and administrative arrangements." The World Medical Association had issued the original Declaration of Helsinki in 1964 and an amended version in 1975. The outcome of the CIOMS / WHO undertaking was, in 1982, Proposed International Ethical Guidelines for Biomedical Research Involving Human Subjects.

The period that followed saw the outbreak of the HIV / AIDS pandemic and proposals to undertake large-scale trials of vaccine and treatment drugs for the condition. These raised new ethical issues that had not been considered

in the preparation of Proposed Guidelines. There were other factors also—rapid advances in medicine and biotechnology, changing research practices such as multinational field trials, experimentation involving vulnerable population groups, and also a changing view, in rich and poor countries, that research involving human subjects was largely beneficial and not threatening. The Declaration of Helsinki was revised twice in the 1980s—in 1983 and 1989. It was timely to revise and update the 1982 guidelines, and CIOMS, with the cooperation of WHO and its Global Programme on AIDS, undertook the task. The outcome was the issuing of two sets of guidelines: in 1991, International Guidelines for Ethical Review of Epidemiological Studies; and, in 1993, International Ethical Guidelines for Biomedical Research Involving Human Subjects.

After 1993, ethical issues arose for which the CIOMS Guidelines had no specific provision. They related mainly to controlled clinical trials, with external sponsors and investigators, carried out in low-resource countries and to the use of comparators other than an established effective intervention. The issue in question was the perceived need in those countries for low-cost, technologically appropriate, public-health solutions, and in particular for HIV/AIDS treatment drugs or vaccines that poorer countries could afford. Commentators took opposing sides on this issue. One advocated, for low-resource countries, trials of interventions that, while they might be less effective than the treatment available in the better-off countries, would be less expensive. All research efforts for public solutions appropriate to developing countries should not be rejected as unethical, they claimed. The research context should be considered. Local decision-making should be the norm. Paternalism on the part of the richer countries towards poorer countries should be avoided. The challenge was to encourage research for local solutions to the burden of disease in much of the world, while providing clear guidance on protecting against exploitation of vulnerable communities and individuals.

The other side argued that such trials constituted, or risked constituting, exploitation of poor countries by rich countries and were inherently unethical. Economic factors should not influence ethical considerations. It was within the capacity of rich countries or the pharmaceutical industry to make established effective treatment available for comparator purposes. Certain low-resource countries had already made available from their own resources established effective treatment for their HIV/AIDS patients.

This conflict complicated the revision and updating of the 1993 Guidelines. Ultimately, it became clear that the conflicting views could not be reconciled, though the proponents of the former view claimed that the new guidelines had built in effective safeguards against exploitation. The commentary to the Guideline concerned (11) recognizes the unresolved, or unresolvable, conflict.

The revision/updating of the 1993 Guidelines began in December 1998, and a first draft prepared by the CIOMS consultant for the project was reviewed by the project steering committee, which met in May 1999. The committee proposed amendments and listed topics on which new or revised guidelines were indicated; it recommended papers to be commissioned on the topics, as well as authors and commentators, for presentation and discussion at a CIOMS interim consultation. It was considered that an interim consultation meeting, of members of the steering committee together with the authors of commissioned papers and designated commentators, followed by further redrafting and electronic distribution and feedback, would better serve the purpose of the project than the process originally envisaged, which had been to complete the revision in one further step. The consultation was accordingly organized for March 2000, in Geneva.

At the consultation, progress on the revision was reported and contentious matters reviewed. Eight commissioned papers previously distributed were presented, commented upon, and discussed. The work of the consultation continued with ad hoc electronic working groups over the following several weeks, and the outcome was made available for the preparation of the third draft. The material commissioned for the consultation was made the subject of a CIOMS publication: *Biomedical Research Ethics: Updating International Guidelines. A Consultation* (December 2000).

An informal redrafting group of eight, from Africa, Asia, Latin America, the United States and the CIOMS secretariat met in New York City in January 2001, and subsequently interacted electronically with one another and with the CIOMS secretariat. A revised draft was posted on the CIOMS website in June 2001 and otherwise widely distributed. Many organizations and individuals commented, some extensively, some critically. Views on certain positions, notably on placebo-controlled trials, were contradictory. For the subsequent revision two members were added to the redrafting group, from Europe and Latin America. The consequent draft was posted on the website in January 2002 in preparation for the CIOMS Conference in February/March 2002.

The CIOMS Conference was convened to discuss and, as far as possible, endorse a final draft to be submitted for final approval to the CIOMS Executive Committee. Besides representation of member organizations of CIOMS, participants included experts in ethics and research from all continents. They reviewed the draft guidelines seriatim and suggested modifications. Guideline 11, Choice of control in clinical trials, was redrafted at the conference in an effort to reduce disagreement. The redrafted text of that guideline was intensively discussed and generally well received. Some participants, however, continued to question the ethical acceptability of the exception to the general rule limiting the use of placebo to the conditions set out in the guideline; they argued that research subjects should not be exposed to risk of serious or irreversible harm when an established effective intervention could prevent such harm, and that such exposure could constitute exploitation. Ultimately, the commentary of Guideline 11 reflects the oppos-

ing positions on use of a comparator other than an established effective intervention for control purposes.

The new text, the 2002 text, which supersedes that of 1993, consists of a statement of general ethical principles, a preamble and 21 guidelines, with an introduction and a brief account of earlier declarations and guidelines. Like the 1982 and 1993 Guidelines, the present publication is designed to be of use, particularly to low-resource countries, in defining national policies on the ethics of biomedical research, applying ethical standards in local circumstances, and establishing or redefining adequate mechanisms for ethical review of research involving human subjects

Comments on the Guidelines are welcome and should be addressed to the Secretary-General, Council for International Organizations of Medical Sciences, c/o World Health Organization, CH-1211 Geneva 27, Switzerland; or by e-mail to cioms@who.int.

INTRODUCTION

This is the third in the series of international ethical guidelines for biomedical research involving human subjects issued by the Council for International Organizations of Medical Sciences since 1982. Its scope and preparation reflect well the transformation that has occurred in the field of research ethics in the almost quarter century since CIOMS first undertook to make this contribution to medical sciences and the ethics of research. The CIOMS Guidelines, with their stated concern for the application of the Declaration of Helsinki in developing countries, necessarily reflect the conditions and the needs of biomedical research in those countries, and the implications for multinational or transnational research in which they may be partners.

An issue, mainly for those countries and perhaps less pertinent now than in the past, has been the extent to which ethical principles are considered universal or as culturally relative—the universalist versus the pluralist view. The challenge to international research ethics is to apply universal ethical principles to biomedical research in a multicultural world with a multiplicity of health-care systems and considerable variation in standards of health care. The Guidelines take the position that research involving human subjects must not violate any universally applicable ethical standards, but acknowledge that, in superficial aspects, the application of the ethical principles, e.g., in relation to individual autonomy and informed consent, needs to take account of cultural values, while respecting absolutely the ethical standards.

Related to this issue is that of the human rights of research subjects, as well as of health professionals as researchers in a variety of sociocultural contexts, and the contribution that international human rights instruments can make in the application of the general principles of ethics to research involving human subjects. The issue concerns largely, though not exclusively, two principles: respect for autonomy and protection of dependent or vulnerable persons and populations. In the preparation of the Guidelines the potential contribution in these respects of human rights instruments and norms was discussed, and the Guideline drafters have represented the views of commentators on safeguarding the corresponding rights of subjects.

Certain areas of research are not represented by specific guidelines. One such is human genetics. It is, however, considered in Guideline 18 Commentary under Issues of confidentiality in genetics research. The ethics of genetics research was the subject of a commissioned paper and commentary.

Another unrepresented area is research with products of conception (embryo and fetal research, and fetal tissue research). An attempt to craft a guideline on the topic proved unfeasible. At issue was the moral status of embryos and fetuses and the degree to which risks to the life or well-being of these entities are ethically permissible.

In relation to the use of comparators in controls, commentators have raised the the question of standard of care to be provided to a control group. They emphasize that standard of care refers to more than the comparator drug or other intervention, and that research subjects in the poorer countries do not usually enjoy the same standard of all-round care enjoyed by subjects in richer countries. This issue is not addressed specifically in the Guidelines.

In one respect the Guidelines depart from the terminology of the Declaration of Helsinki. 'Best current intervention' is the term most commonly used to describe the active comparator that is ethically preferred in controlled clinical trials. For many indications, however, there is more than one established 'current' intervention and expert clinicians do not agree on which is superior. In other circumstances in which there are several established 'current' interventions, some expert clinicians recognize one as superior to the rest; some commonly prescribe another because the superior intervention may be locally unavailable, for example, or prohibitively expensive or unsuited to the capability of particular patients to adhere to a complex and rigorous regimen. 'Established effective intervention' is the term used in Guideline 11 to refer to all such interventions, including the best and the various alternatives to the best. In some cases an ethical review committee may determine that it is ethically acceptable to use an established effective intervention as a comparator, even in cases where such an intervention is not considered the best current intervention.

The mere formulation of ethical guidelines for biomedical research involving human subjects will hardly resolve all the moral doubts that can arise in association with much research, but the Guidelines can at least draw the attention of sponsors, investigators and ethical review committees to the need to consider carefully the ethical implications of research protocols and the conduct of research, and thus conduce to high scientific and ethical standards of biomedical research.

INTERNATIONAL INSTRUMENTS AND GUIDELINES

The first international instrument on the ethics of medical research, the Nuremberg Code, was promulgated in 1947 as a consequence of the trial of physicians (the Doctors' Trial) who had conducted atrocious experiments on unconsenting prisoners and detainees during the second world war. The Code, designed to protect the integrity of the research subject, set out conditions for the ethical conduct of research involving human subjects, emphasizing their voluntary consent to research.

The Universal Declaration of Human Rights was adopted by the General Assembly of the United Nations in 1948. To give the Declaration legal as well as moral force, the General Assembly adopted in 1966 the International Covenant on Civil and Political Rights. Article 7 of the Covenant states "No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment. In particular, no one shall be subjected without his free consent to medical or scientific experimentation". It is through this statement that society expresses the fundamental human value that is held to govern all research involving human subjects—the protection of the rights and welfare of all human subjects of scientific experimentation.

The Declaration of Helsinki, issued by the World Medical Association in 1964, is the fundamental document in the field of ethics in biomedical research and has influenced the formulation of international, regional and national legislation and codes of conduct. The Declaration, amended several times, most recently in 2000 (Appendix 2), is a comprehensive international statement of the ethics of research involving human subjects. It sets out ethical guidelines for physicians engaged in both clinical and nonclinical biomedical research.

Since the publication of the CIOMS 1993 Guidelines, several international organizations have issued ethical guidance on clinical trials. This has included, from the World Health Organization, in 1995, Guidelines for Good Clinical Practice for Trials on Pharmaceutical Products; and from the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), in 1996, Guideline on Good Clinical Practice, designed to ensure that data generated from clinical trials are mutually acceptable to regulatory authorities in the European Union, Japan and the United States of America. The Joint United Nations Programme on HIV / AIDS published in 2000 the UNAIDS Guidance Document Ethical Considerations in HIV Preventive Vaccine Research.

In 2001 the Council of Ministers of the European Union adopted a Directive on clinical trials, which will be binding in law in the countries of the Union from 2004. The Council of Europe, with more than 40 member States, is developing a Protocol on Biomedical Research, which will be an additional protocol to the Council's 1997 Convention on Human Rights and Biomedicine.

Not specifically concerned with biomedical research involving human subjects but clearly pertinent, as noted above, are international human rights instruments. These are mainly the Universal Declaration of Human Rights, which, particularly in its science provisions, was highly influenced by the Nuremberg Code; the International Covenant on Civil and Political Rights; and the International Covenant on Economic, Social and Cultural Rights. Since the Nuremberg experience, human rights law has expanded to include the protection of women (Convention on the Elimination of All Forms of Discrimination Against Women) and children (Convention on the Rights of the Child). These and other such international instruments endorse in terms of human rights the general ethical principles that underlie the CIOMS International Ethical Guidelines.

GENERAL ETHICAL PRINCIPLES

All research involving human subjects should be conducted in accordance with three basic ethical principles, namely respect for persons, beneficence and justice. It is generally agreed that these principles, which in the abstract have equal moral force, guide the conscientious preparation of proposals for scientific studies. In varying circumstances they may be expressed differently and given different moral weight, and their application may lead to different decisions or courses of action. The present guidelines are directed at the application of these principles to research involving human subjects.

Respect for persons incorporates at least two fundamental ethical considerations, namely:

- (a) respect for autonomy, which requires that those who are capable of deliberation about their personal choices should be treated with respect for their capacity for self-determination; and
- (b) protection of persons with impaired or diminished autonomy, which requires that those who are dependent or vulnerable be afforded security against harm or abuse.

Beneficence refers to the ethical obligation to maximize benefits and to minimize harms. This principle gives rise to norms requiring that the risks of research be reasonable in the light of the expected benefits, that the research design be sound, and that the investigators be competent both to conduct the research and to safeguard the welfare of the research subjects. Beneficence further proscribes the deliberate infliction of harm on persons; this aspect of beneficence is sometimes expressed as a separate principle, nonmaleficence (do no harm).

Justice refers to the ethical obligation to treat each person in accordance with what is morally right and proper, to give each person what is due to him or her. In the ethics of research involving human subjects the principle refers primarily to distributive justice, which requires the equitable distribution of both the burdens and the benefits of participation in research. Differences in distribution of burdens and benefits are justifiable only if they are based on morally relevant distinctions between persons; one such distinction is vulnerability. "Vulnerability" refers to a substantial incapacity to protect one's own interests owing to such impediments as lack of capability to give informed consent, lack of alternative means of obtaining medical care or other expensive necessities, or being a junior or subordinate member of a hierarchical group. Accordingly, special provision must be made for the protection of the rights and welfare of vulnerable persons.

Sponsors of research or investigators cannot, in general, be held accountable for unjust conditions where the research is conducted, but they must refrain from practices that are likely to worsen unjust conditions or contribute to new inequities. Neither should they take advantage of the relative inability of low-resource countries or vulnerable populations to protect their own interests, by conducting research inexpensively and avoiding complex regulatory systems of industrialized countries in order to develop products for the lucrative markets of those countries.

In general, the research project should leave low-resource countries or communities better off than previously or, at least, no worse off. It should be responsive to their health needs and priorities in that any product developed is made reasonably available to them, and as far as possible leave the population in a better position to obtain effective health care and protect its own health.

Justice requires also that the research be responsive to the health conditions or needs of vulnerable subjects. The subjects selected should be the least vulnerable necessary to accomplish the purposes of the research. Risk to vulnerable subjects is most easily justified when it arises from interventions or procedures that hold out for them the prospect of direct health-related benefit. Risk that does not hold out such prospect must be justified by the anticipated benefit to the population of which the individual research subject is representative.

PREAMBLE

The term "research" refers to a class of activity designed to develop or contribute to generalizable knowledge. Generalizable knowledge consists of theories, principles or relationships, or the accumulation of information on which they are based, that can be corroborated by accepted scientific methods of observation and inference. In the present context "research" includes both medical and behavioural studies pertaining to human health. Usually "research" is modified by the adjective "biomedical" to indicate its relation to health.

Progress in medical care and disease prevention depends upon an understanding of physiological and pathological processes or epidemiological findings, and requires at some time research involving human subjects. The collection, analysis and interpretation of information obtained from research involving human beings contribute significantly to the improvement of human health.

Research involving human subjects includes:

- studies of a physiological, biochemical or pathological process, or of the response to a specific intervention—whether physical, chemical or psychological—in healthy subjects or patients;
- controlled trials of diagnostic, preventive or therapeutic measures in larger groups of persons, designed to demonstrate a specific generalizable response to these measures against a background of individual biological variation;
- studies designed to determine the consequences for individuals and communities of specific preventive or therapeutic measures; and
- studies concerning human health-related behaviour in a variety of circumstances and environments.

Research involving human subjects may employ either observation or physical, chemical or psychological intervention; it may also either generate records or make use of existing records containing biomedical or other information about individuals who may or may not be identifiable from the records or information. The use of such records and the protection of the confidentiality of data obtained from those records are discussed in International Guidelines for Ethical Review of Epidemiological Studies (CIOMS, 1991).

The research may be concerned with the social environment, manipulating environmental factors in a way that could affect incidentally-exposed individuals. It is defined in broad terms in order to embrace field studies of pathogenic organisms and toxic chemicals under investigation for health-related purposes.

Biomedical research with human subjects is to be distinguished from the practice of medicine, public health and other forms of health care, which is designed to contribute directly to the health of individuals or communities. Prospective subjects may find it confusing when research and practice are to be conducted simultaneously, as when research is designed to obtain new information about the efficacy of a drug or other therapeutic, diagnostic or preventive modality.

As stated in Paragraph 32 of the Declaration of Helsinki, "In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed."

Professionals whose roles combine investigation and treatment have a special obligation to protect the rights and welfare of the patient-subjects. An investigator who agrees to act as physician-investigator undertakes some or all of the legal and ethical responsibilities of the subject's primary-care physician. In such a case, if the subject withdraws from the research owing to complications related to the research or in the exercise of the right to withdraw without loss of benefit, the physician has an obligation to continue to provide medical care, or to see that the subject receives the necessary care in the health-care system, or to offer assistance in finding another physician.

Research with human subjects should be carried out only by, or strictly supervised by, suitably qualified and experienced investigators and in accordance with a protocol that clearly states: the aim of the research; the reasons for proposing that it involve human subjects; the nature and degree of any known risks to the subjects; the sources from which it is proposed to recruit subjects; and the means proposed for ensuring that subjects' consent will be adequately informed and voluntary. The protocol should be scientifically and ethically appraised by one or more suitably constituted review bodies, independent of the investigators.

New vaccines and medicinal drugs, before being approved for general use, must be tested on human subjects in clinical trials; such trials constitute a substantial part of all research involving human subjects.

THE GUIDELINES

Guideline 1: Ethical justification and scientific validity of biomedical research involving human beings

The ethical justification of biomedical research involving human subjects is the prospect of discovering new ways of benefiting people's health. Such research can be ethically justifiable only if it is carried out in ways that respect and protect, and are fair to, the subjects of that research and are morally acceptable within the communities in which the research is carried out. Moreover, because scientifically invalid research is unethical in that it exposes research subjects to risks without possible benefit, investigators and sponsors must ensure that proposed studies involving human subjects conform to generally accepted scientific principles and are based on adequate knowledge of the pertinent scientific literature.

Commentary on Guideline 1: Among the essential features of ethically justified research involving human subjects, including research with identifiable human tissue or data, are that the research offers a means of developing information not otherwise obtainable, that the design of the research is scientifically sound, and that the investigators and other research personnel are competent. The methods to be used should be appropriate to the objectives of the research and the field of study. Investigators and sponsors must also ensure that all who participate in the conduct of the research are qualified by virtue of their education and experience to perform competently in their roles. These considerations should be adequately reflected in the research protocol submitted for review and clearance to scientific and ethical review committees (Appendix I). Scientific review is discussed further in the Commentaries to Guidelines 2 and 3: Ethical review committees and Ethical review of externally sponsored research. Other ethical aspects of research are discussed in the remaining guidelines and their commentaries. The protocol designed for submission for review and clearance to scientific and ethical review committees should include, when relevant, the items specified in Appendix I, and should be carefully followed in conducting the research.

Guideline 2: Ethical review committees

All proposals to conduct research involving human subjects must be submitted for review of their scientific merit and ethical acceptability to one or more scientific review and ethical review committees. The review committees must be independent of the research team, and any direct financial or other material benefit they may derive from the research should not be contingent on the outcome of their review. The investigator must obtain their approval or clearance before undertaking the research. The ethical review committee should conduct further reviews as necessary in the course of the research, including monitoring of the progress of the study.

Commentary on Guideline 2: Ethical review committees may function at the institutional, local, regional, or national level, and in some cases at the international level. The regulatory or other governmental authorities concerned should promote uniform standards across committees within a country, and, under all systems, sponsors of research and institutions in which the investigators are employed should allocate sufficient resources to the review process. Ethical review committees may receive money for the activity of reviewing protocols, but under no circumstances may payment be offered or accepted for a review committee's approval or clearance of a protocol.

Scientific review. According to the Declaration of Helsinki (Paragraph 11), medical research involving humans must conform to generally accepted scientific principles, and be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, where indicated, animal experimental-

tion. Scientific review must consider, *inter alia*, the study design, including the provisions for avoiding or minimizing risk and for monitoring safety. Committees competent to review and approve scientific aspects of research proposals must be multidisciplinary.

Ethical review. The ethical review committee is responsible for safeguarding the rights, safety, and well-being of the research subjects. Scientific review and ethical review cannot be separated: scientifically unsound research involving humans as subjects is *ipso facto* unethical in that it may expose them to risk or inconvenience to no purpose; even if there is no risk of injury, wasting of subjects' and researchers' time in unproductive activities represents loss of a valuable resource. Normally, therefore, an ethical review committee considers both the scientific and the ethical aspects of proposed research. It must either carry out a proper scientific review or verify that a competent expert body has determined that the research is scientifically sound. Also, it considers provisions for monitoring of data and safety. If the ethical review committee finds a research proposal scientifically sound, or verifies that a competent expert body has found it so, it should then consider whether any known or possible risks to the subjects are justified by the expected benefits, direct or indirect, and whether the proposed research methods will minimize harm and maximize benefit. (See Guideline 8: Benefits and risks of study participation.) If the proposal is sound and the balance of risks to anticipated benefits is reasonable, the committee should then determine whether the procedures proposed for obtaining informed consent are satisfactory and those proposed for the selection of subjects are equitable.

Ethical review of emergency compassionate use of an investigational therapy. In some countries, drug regulatory authorities require that the so-called compassionate or humanitarian use of an investigational treatment be reviewed by an ethical review committee as though it were research. Exceptionally, a physician may undertake the compassionate use of an investigational therapy before obtaining the approval or clearance of an ethical review committee, provided three criteria are met: a patient needs emergency treatment, there is some evidence of possible effectiveness of the investigational treatment, and there is no other treatment available that is known to be equally effective or superior. Informed consent should be obtained according to the legal requirements and cultural standards of the community in which the intervention is carried out. Within one week the physician must report to the ethical review committee the details of the case and the action taken, and an independent health-care professional must confirm in writing to the ethical review committee the treating physician's judgment that the use of the investigational intervention was justified according to the three specified criteria. (See also Guideline 13 Commentary section: Other vulnerable groups.)

National (centralized) or local review. Ethical review committees may be created under the aegis of national or local health administrations, national (or centralized) medical research councils or other nationally representative bodies. In a highly centralized administration a national, or centralized, review committee may be constituted for both the scientific and the ethical review of research protocols. In countries where medical research is not centrally administered, ethical review is more effectively and conveniently undertaken at a local or regional level. The authority of a local ethical review committee may be confined to a single institution or may extend to all institutions in which biomedical research is carried out within a defined geographical area. The basic responsibilities of ethical review committees are:

- to determine that all proposed interventions, particularly the administration of drugs and vaccines or the use of medical devices or procedures under development, are acceptably safe to be undertaken in humans or to verify that another competent expert body has done so;
- to determine that the proposed research is scientifically sound or to verify that another competent expert body has done so;
- to ensure that all other ethical concerns arising from a protocol are satisfactorily resolved both in principle and in practice;
- to consider the qualifications of the investigators, including education in the principles of research practice, and the conditions of the research site with a view to ensuring the safe conduct of the trial; and
- to keep records of decisions and to take measures to follow up on the conduct of ongoing research projects.

Committee membership. National or local ethical review committees should be so composed as to be able to provide complete and adequate review of the research proposals submitted to them. It is generally presumed that their membership should include physicians, scientists and other professionals such as nurses, lawyers, ethicists and clergy, as well as lay persons qualified to represent the cultural and moral values of the community and to ensure that the rights of the research subjects will be respected. They should include both men and women. When uneducated or illiterate persons form the focus of a study they should also be considered for membership or invited to be represented and have their views expressed. A number of members should be replaced periodically with the aim of blending the advantages of experience with those of fresh perspectives. A national or local ethical review committee responsible for reviewing and approving proposals for externally sponsored research should have among its members or consultants persons who are thoroughly familiar with the customs and traditions of the population or community concerned and sensitive to issues of human dignity. Committees that often review research proposals directed at specific diseases or impairments, such as HIV / AIDS or paraplegia, should invite or hear the views of individuals or

bodies representing patients with such diseases or impairments. Similarly, for research involving such subjects as children, students, elderly persons or employees, committees should invite or hear the views of their representatives or advocates. To maintain the review committee's independence from the investigators and sponsors and to avoid conflict of interest, any member with a special or particular, direct or indirect, interest in a proposal should not take part in its assessment if that interest could subvert the member's objective judgment. Members of ethical review committees should be held to the same standard of disclosure as scientific and medical research staff with regard to financial or other interests that could be construed as conflicts of interest. A practical way of avoiding such conflict of interest is for the committee to insist on a declaration of possible conflict of interest by any of its members. A member who makes such a declaration should then withdraw, if to do so is clearly the appropriate action to take, either at the member's own discretion or at the request of the other members. Before withdrawing, the member should be permitted to offer comments on the protocol or to respond to questions of other members.

Multi-centre research. Some research projects are designed to be conducted in a number of centres in different communities or countries. Generally, to ensure that the results will be valid, the study must be conducted in an identical way at each centre. Such studies include clinical trials, research designed for the evaluation of health service programmes, and various kinds of epidemiological research. For such studies, local ethical or scientific review committees are not normally authorized to change doses of drugs, to change inclusion or exclusion criteria, or to make other similar modifications. They should be fully empowered to prevent a study that they believe to be unethical. Moreover, changes that local review committees believe are necessary to protect the research subjects should be documented and reported to the research institution or sponsor responsible for the whole research programme for consideration and due action, to ensure that all other subjects can be protected and that the research will be valid across sites. To ensure the validity of multi-centre research, any change in the protocol should be made at every collaborating centre or institution, or, failing this, explicit inter-centre comparability procedures must be introduced; changes made at some but not all will defeat the purpose of multi-centre research. For some multi-centre studies, scientific and ethical review may be facilitated by agreement among centres to accept the conclusions of a single review committee; its members could include a representative of the ethical review committee at each of the centres at which the research is to be conducted, as well as individuals competent to conduct scientific review. In other circumstances, a centralized review may be complemented by local review relating to the local participating investigators and institutions. The central committee could review the study from a scientific and ethical standpoint, and the local committees could verify the practicability of the study in their communities, including the infrastructures, the state of training, and ethical considerations of local significance. In a large multi-centre trial, individual investigators will not have authority to act independently, with regard to data analysis or to preparation and publication of manuscripts, for instance. Such a trial usually has a set of committees which operate under the direction of a steering committee and are responsible for such functions and decisions. The function of the ethical review committee in such cases is to review the relevant plans with the aim of avoiding abuses.

Sanctions. Ethical review committees generally have no authority to impose sanctions on researchers who violate ethical standards in the conduct of research involving humans. They may, however, withdraw ethical approval of a research project if judged necessary. They should be required to monitor the implementation of an approved protocol and its progression, and to report to institutional or governmental authorities any serious or continuing non-compliance with ethical standards as they are reflected in protocols that they have approved or in the conduct of the studies. Failure to submit a protocol to the committee should be considered a clear and serious violation of ethical standards. Sanctions imposed by governmental, institutional, professional or other authorities possessing disciplinary power should be employed as a last resort. Preferred methods of control include cultivation of an atmosphere of mutual trust, and education and support to promote in researchers and in sponsors the capacity for ethical conduct of research. Should sanctions become necessary, they should be directed at the non-compliant researchers or sponsors. They may include fines or suspension of eligibility to receive research funding, to use investigational interventions, or to practise medicine. Unless there are persuasive reasons to do otherwise, editors should refuse to publish the results of research conducted unethically, and retract any articles that are subsequently found to contain falsified or fabricated data or to have been based on unethical research. Drug regulatory authorities should consider refusal to accept unethically obtained data submitted in support of an application for authorization to market a product. Such sanctions, however, may deprive of benefit not only the errant researcher or sponsor but also that segment of society intended to benefit from the research; such possible consequences merit careful consideration.

Potential conflicts of interest related to project support. Increasingly, biomedical studies receive funding from commercial firms. Such sponsors have good reasons to support research methods that are ethically and scientifically acceptable, but cases have arisen in which the conditions of funding could have introduced bias. It may happen that investigators have little or no input into trial design, limited access to the raw data, or limited participation in data interpretation, or that the results of a clinical trial may not be published if they are unfavourable to the sponsor's product. This risk of bias may also be associated with other sources of support, such as government or foundations. As the persons directly responsible for their work, investigators should not enter into agreements that interfere unduly with their access to the data or their ability to analyse the data independently, to prepare manuscripts, or to publish them. Investigators must also disclose potential or apparent conflicts of interest on their part to the ethical

review committee or to other institutional committees designed to evaluate and manage such conflicts. Ethical review committees should therefore ensure that these conditions are met. See also Multi-centre research, above.

Guideline 3: Ethical review of externally sponsored research

An external sponsoring organization and individual investigators should submit the research protocol for ethical and scientific review in the country of the sponsoring organization, and the ethical standards applied should be no less stringent than they would be for research carried out in that country. The health authorities of the host country, as well as a national or local ethical review committee, should ensure that the proposed research is responsive to the health needs and priorities of the host country and meets the requisite ethical standards.

Commentary on Guideline 3:

Definition. The term externally sponsored research refers to research undertaken in a host country but sponsored, financed, and sometimes wholly or partly carried out by an external international or national organization or pharmaceutical company with the collaboration or agreement of the appropriate authorities, institutions and personnel of the host country.

Ethical and scientific review. Committees in both the country of the sponsor and the host country have responsibility for conducting both scientific and ethical review, as well as the authority to withhold approval of research proposals that fail to meet their scientific or ethical standards. As far as possible, there must be assurance that the review is independent and that there is no conflict of interest that might affect the judgement of members of the review committees in relation to any aspect of the research. When the external sponsor is an international organization, its review of the research protocol must be in accordance with its own independent ethical-review procedures and standards. Committees in the external sponsoring country or international organization have a special responsibility to determine whether the scientific methods are sound and suitable to the aims of the research; whether the drugs, vaccines, devices or procedures to be studied meet adequate standards of safety; whether there is sound justification for conducting the research in the host country rather than in the country of the external sponsor or in another country; and whether the proposed research is in compliance with the ethical standards of the external sponsoring country or international organization. Committees in the host country have a special responsibility to determine whether the objectives of the research are responsive to the health needs and priorities of that country. The ability to judge the ethical acceptability of various aspects of a research proposal requires a thorough understanding of a community's customs and traditions. The ethical review committee in the host country, therefore, must have as either members or consultants persons with such understanding; it will then be in a favourable position to determine the acceptability of the proposed means of obtaining informed consent and otherwise respecting the rights of prospective subjects as well as of the means proposed to protect the welfare of the research subjects. Such persons should be able, for example, to indicate suitable members of the community to serve as intermediaries between investigators and subjects, and to advise on whether material benefits or inducements may be regarded as appropriate in the light of a community's gift-exchange and other customs and traditions. When a sponsor or investigator in one country proposes to carry out research in another, the ethical review committees in the two countries may, by agreement, undertake to review different aspects of the research protocol. In short, in respect of host countries either with developed capacity for independent ethical review or in which external sponsors and investigators are contributing substantially to such capacity, ethical review in the external, sponsoring country may be limited to ensuring compliance with broadly stated ethical standards. The ethical review committee in the host country can be expected to have greater competence for reviewing the detailed plans for compliance, in view of its better understanding of the cultural and moral values of the population in which it is proposed to conduct the research; it is also likely to be in a better position to monitor compliance in the course of a study. However, in respect of research in host countries with inadequate capacity for independent ethical review, full review by the ethical review committee in the external sponsoring country or international agency is necessary.

Guideline 4: Individual informed consent

For all biomedical research involving humans the investigator must obtain the voluntary informed consent of the prospective subject or, in the case of an individual who is not capable of giving informed consent, the permission of a legally authorized representative in accordance with applicable law. Waiver of informed consent is to be regarded as uncommon and exceptional, and must in all cases be approved by an ethical review committee.

Commentary on Guideline 4:

General considerations. Informed consent is a decision to participate in research, taken by a competent individual who has received the necessary information; who has adequately understood the information; and who, after considering the information, has arrived at a decision without having been subjected to coercion, undue influence or inducement, or intimidation. Informed consent is based on the principle that competent individuals are entitled to choose freely whether to participate in research. Informed consent protects the individual's freedom of choice and respects the individual's autonomy. As an additional safeguard, it must always be complemented by independent ethical review of research proposals. This safeguard of independent review is particularly important as many individuals are limited in their capacity to give adequate informed consent; they include young children, adults with severe mental or behavioural disorders, and persons who are unfamiliar with medical concepts and technology (See Guidelines 13, 14, 15).

Process. Obtaining informed consent is a process that is begun when initial contact is made with a prospective subject and continues throughout the course of the study. By informing the prospective subjects, by repetition and explanation, by answering their questions as they arise, and by ensuring that each individual understands each procedure, investigators elicit their informed consent and in so doing manifest respect for their dignity and autonomy. Each individual must be given as much time as is needed to reach a decision, including time for consultation with family members or others. Adequate time and resources should be set aside for informed-consent procedures.

Language. Informing the individual subject must not be simply a ritual recitation of the contents of a written document. Rather, the investigator must convey the information, whether orally or in writing, in language that suits the individual's level of understanding. The investigator must bear in mind that the prospective subject's ability to understand the information necessary to give informed consent depends on that individual's maturity, intelligence, education and belief system. It depends also on the investigator's ability and willingness to communicate with patience and sensitivity.

Comprehension. The investigator must then ensure that the prospective subject has adequately understood the information. The investigator should give each one full opportunity to ask questions and should answer them honestly, promptly and completely. In some instances the investigator may administer an oral or a written test or otherwise determine whether the information has been adequately understood.

Documentation of consent. Consent may be indicated in a number of ways. The subject may imply consent by voluntary actions, express consent orally, or sign a consent form. As a general rule, the subject should sign a consent form, or, in the case of incompetence, a legal guardian or other duly authorized representative should do so. The ethical review committee may approve waiver of the requirement of a signed consent form if the research carries no more than minimal risk—that is, risk that is no more likely and not greater than that attached to routine medical or psychological examination—and if the procedures to be used are only those for which signed consent forms are not customarily required outside the research context. Such waivers may also be approved when existence of a signed consent form would be an unjustified threat to the subject's confidentiality. In some cases, particularly when the information is complicated, it is advisable to give subjects information sheets to retain; these may resemble consent forms in all respects except that subjects are not required to sign them. Their wording should be cleared by the ethical review committee. When consent has been obtained orally, investigators are responsible for providing documentation or proof of consent.

Waiver of the consent requirement. Investigators should never initiate research involving human subjects without obtaining each subject's informed consent, unless they have received explicit approval to do so from an ethical review committee. However, when the research design involves no more than minimal risk and a requirement of individual informed consent would make the conduct of the research impracticable (for example, where the research involves only excerpting data from subjects' records), the ethical review committee may waive some or all of the elements of informed consent.

Renewing consent. When material changes occur in the conditions or the procedures of a study, and also periodically in long-term studies, the investigator should once again seek informed consent from the subjects. For example, new information may have come to light, either from the study or from other sources, about the risks or benefits of products being tested or about alternatives to them. Subjects should be given such information promptly. In many clinical trials, results are not disclosed to subjects and investigators until the study is concluded. This is ethically acceptable if an ethical review committee has approved their non-disclosure.

Cultural considerations. In some cultures an investigator may enter a community to conduct research or approach prospective subjects for their individual consent only after obtaining permission from a community leader, a council of elders, or another designated authority. Such customs must be respected. In no case, however, may the permission of a community leader or other authority substitute for individual informed consent. In some populations the use of a number of local languages may complicate the communication of information to potential subjects and the ability of an investigator to ensure that they truly understand it. Many people in all cultures are unfamiliar with, or do not readily understand, scientific concepts such as those of placebo or randomization. Sponsors and investigators should develop culturally appropriate ways to communicate information that is necessary for adherence to the standard required in the informed consent process. Also, they should describe and justify in the research protocol the procedure they plan to use in communicating information to subjects. For collaborative research in developing countries the research project should, if necessary, include the provision of resources to ensure that informed consent can indeed be obtained legitimately within different linguistic and cultural settings.

Consent to use for research purposes biological materials (including genetic material) from subjects in clinical trials. Consent forms for the research protocol should include a separate section for clinical-trial subjects who are requested to provide their consent for the use of their biological specimens for research. Separate consent may be appropriate in some cases (e.g., if investigators are requesting permission to conduct basic research which is not a necessary part of the clinical trial), but not in others (e.g., the clinical trial requires the use of subjects' biological materials).

Use of medical records and biological specimens. Medical records and biological specimens taken in the course of clinical care may be used for research without the consent of the patients/subjects only if an ethical review com-

mittee has determined that the research poses minimal risk, that the rights or interests of the patients will not be violated, that their privacy and confidentiality or anonymity are assured, and that the research is designed to answer an important question and would be impracticable if the requirement for informed consent were to be imposed. Patients have a right to know that their records or specimens may be used for research. Refusal or reluctance of individuals to agree to participate would not be evidence of impracticability sufficient to warrant waiving informed consent. Records and specimens of individuals who have specifically rejected such uses in the past may be used only in the case of public health emergencies. (See Guideline 18 Commentary, Confidentiality between physician and patient.)

Secondary use of research records or biological specimens. Investigators may want to use records or biological specimens that another investigator has used or collected for use, in another institution in the same or another country. This raises the issue of whether the records or specimens contain personal identifiers, or can be linked to such identifiers, and by whom. (See also Guideline 18: Safeguarding confidentiality.) If informed consent or permission was required to authorize the original collection or use of such records or specimens for research purposes, secondary uses are generally constrained by the conditions specified in the original consent. Consequently, it is essential that the original consent process anticipate, to the extent that this is feasible, any foreseeable plans for future use of the records or specimens for research. Thus, in the original process of seeking informed consent a member of the research team should discuss with, and, when indicated, request the permission of, prospective subjects as to:

- (i) whether there will or could be any secondary use and, if so, whether such secondary use will be limited with regard to the type of study that may be performed on such materials;
- (ii) the conditions under which investigators will be required to contact the research subjects for additional authorization for secondary use;
- (iii) the investigators' plans, if any, to destroy or to strip of personal identifiers the records or specimens; and
- (iv) the rights of subjects to request destruction or anonymization of biological specimens or of records or parts of records that they might consider particularly sensitive, such as photographs, videotapes or audiotapes.

(See also Guidelines 5: Obtaining informed consent: Essential information for prospective research subjects; 6: Obtaining informed consent: Obligations of sponsors and investigators; and 7: Inducement to participate.)

Guideline 5: Obtaining informed consent: Essential information for prospective research subjects

Before requesting an individual's consent to participate in research, the investigator must provide the following information, in language or another form of communication that the individual can understand:

- (1) that the individual is invited to participate in research, the reasons for considering the individual suitable for the research, and that participation is voluntary;
- (2) that the individual is free to refuse to participate and will be free to withdraw from the research at any time without penalty or loss of benefits to which he or she would otherwise be entitled;
- (3) the purpose of the research, the procedures to be carried out by the investigator and the subject, and an explanation of how the research differs from routine medical care;
- (4) for controlled trials, an explanation of features of the research design (e.g., randomization, double-blind-ing), and that the subject will not be told of the assigned treatment until the study has been completed and the blind has been broken;
- (5) the expected duration of the individual's participation (including number and duration of visits to the research centre and the total time involved) and the possibility of early termination of the trial or of the individual's participation in it;
- (6) whether money or other forms of material goods will be provided in return for the individual's participation and, if so, the kind and amount;
- (7) that, after the completion of the study, subjects will be informed of the findings of the research in general, and individual subjects will be informed of any finding that relates to their particular health status;
- (8) that subjects have the right of access to their data on demand, even if these data lack immediate clinical utility (unless the ethical review committee has approved temporary or permanent non-disclosure of data, in which case the subject should be informed of, and given, the reasons for such non-disclosure);
- (9) any foreseeable risks, pain or discomfort, or inconvenience to the individual (or others) associated with participation in the research, including risks to the health or well-being of a subject's spouse or partner;
- (10) the direct benefits, if any, expected to result to subjects from participating in the research
- (11) the expected benefits of the research to the community or to society at large, or contributions to scientific knowledge;
- (12) whether, when and how any products or interventions proven by the research to be safe and effective will be made available to subjects after they have completed their participation in the research, and whether they will be expected to pay for them;
- (13) any currently available alternative interventions or courses of treatment;

- (14) the provisions that will be made to ensure respect for the privacy of subjects and for the confidentiality of records in which subjects are identified;
- (15) the limits, legal or other, to the investigators' ability to safeguard confidentiality, and the possible consequences of breaches of confidentiality;
- (16) policy with regard to the use of results of genetic tests and familial genetic information, and the precautions in place to prevent disclosure of the results of a subject's genetic tests
- (17) to immediate family relatives or to others (e.g., insurance companies or employers) without the consent of the subject;
- (18) the sponsors of the research, the institutional affiliation of the investigators, and the nature and sources of funding for the research;
- (19) the possible research uses, direct or secondary, of the subject's medical records and of biological specimens taken in the course of clinical care (See also Guidelines 4 and 18 Commentaries);
- (20) whether it is planned that biological specimens collected in the research will be destroyed at its conclusion, and, if not, details about their storage (where, how, for how long, and final disposition) and possible future use, and that subjects have the right to decide about such future use, to refuse storage, and to have the material destroyed (See Guideline 4 Commentary);
- (21) whether commercial products may be developed from biological specimens, and whether the participant will receive monetary or other benefits from the development of such products;
- (22) whether the investigator is serving only as an investigator or as both investigator and the subject's physician;
- (23) the extent of the investigator's responsibility to provide medical services to the participant;
- (24) that treatment will be provided free of charge for specified types of research-related injury or for complications associated with the research, the nature and duration of such care, the name of the organization or individual that will provide the treatment, and whether there is any uncertainty regarding funding of such treatment;
- (25) in what way, and by what organization, the subject or the subject's family or dependants will be compensated for disability or death resulting from such injury (or, when indicated, that there are no plans to provide such compensation);
- (26) whether or not, in the country in which the prospective subject is invited to participate in research, the right to compensation is legally guaranteed; and
- (27) that an ethical review committee has approved or cleared the research protocol.

Guideline 6: Obtaining informed consent: Obligations of sponsors and investigators

Sponsors and investigators have a duty to:

- refrain from unjustified deception, undue influence, or intimidation;
- seek consent only after ascertaining that the prospective subject has adequate understanding of the relevant facts and of the consequences of participation and has had sufficient opportunity to consider whether to participate;
- as a general rule, obtain from each prospective subject a signed form as evidence of informed consent—investigators should justify any exceptions to this general rule and obtain the approval of the ethical review committee (See Guideline 4 Commentary, Documentation of consent);
- renew the informed consent of each subject if there are significant changes in the conditions or procedures of the research or if new information becomes available that could affect the willingness of subjects to continue to participate; and
- renew the informed consent of each subject in long-term studies at pre-determined intervals, even if there are no changes in the design or objectives of the research.

Commentary on Guideline 6: The investigator is responsible for ensuring the adequacy of informed consent from each subject. The person obtaining informed consent should be knowledgeable about the research and capable of answering questions from prospective subjects. Investigators in charge of the study must make themselves available to answer questions at the request of subjects. Any restrictions on the subject's opportunity to ask questions and receive answers before or during the research undermines the validity of the informed consent. In some types of research, potential subjects should receive counselling about risks of acquiring a disease unless they take precautions. This is especially true of HIV/AIDS vaccine research (UNAIDS Guidance Document Ethical Considerations in HIV Preventive Vaccine Research, Guidance Point 14).

Withholding information and deception. Sometimes, to ensure the validity of research, investigators withhold certain information in the consent process. In biomedical research, this typically takes the form of withholding information about the purpose of specific procedures. For example, subjects in clinical trials are often not told the purpose of tests performed to monitor their compliance with the protocol, since if they knew their compliance was being

monitored they might modify their behaviour and hence invalidate results. In most such cases, the prospective subjects are asked to consent to remain uninformed of the purpose of some procedures until the research is completed; after the conclusion of the study they are given the omitted information. In other cases, because a request for permission to withhold some information would jeopardize the validity of the research, subjects are not told that some information has been withheld until the research has been completed. Any such procedure must receive the explicit approval of the ethical review committee. Active deception of subjects is considerably more controversial than simply withholding certain information. Lying to subjects is a tactic not commonly employed in biomedical research. Social and behavioural scientists, however, sometimes deliberately misinform subjects to study their attitudes and behaviour. For example, scientists have pretended to be patients to study the behaviour of health-care professionals and patients in their natural settings. Some people maintain that active deception is never permissible. Others would permit it in certain circumstances. Deception is not permissible, however, in cases in which the deception itself would disguise the possibility of the subject being exposed to more than minimal risk. When deception is deemed indispensable to the methods of a study the investigators must demonstrate to an ethical review committee that no other research method would suffice; that significant advances could result from the research; and that nothing has been withheld that, if divulged, would cause a reasonable person to refuse to participate. The ethical review committee should determine the consequences for the subject of being deceived, and whether and how deceived subjects should be informed of the deception upon completion of the research. Such informing, commonly called "debriefing," ordinarily entails explaining the reasons for the deception. A subject who disapproves of having been deceived should be offered an opportunity to refuse to allow the investigator to use information thus obtained. Investigators and ethical review committees should be aware that deceiving research subjects may wrong them as well as harm them; subjects may resent not having been informed when they learn that they have participated in a study under false pretences. In some studies there may be justification for deceiving persons other than the subjects by either withholding or disguising elements of information. Such tactics are often proposed, for example, for studies of the abuse of spouses or children. An ethical review committee must review and approve all proposals to deceive persons other than the subjects. Subjects are entitled to prompt and honest answers to their questions; the ethical review committee must determine for each study whether others who are to be deceived are similarly entitled.

Intimidation and undue influence. Intimidation in any form invalidates informed consent. Prospective subjects who are patients often depend for medical care upon the physician/investigator, who consequently has a certain credibility in their eyes, and whose influence over them may be considerable, particularly if the study protocol has a therapeutic component. They may fear, for example, that refusal to participate would damage the therapeutic relationship or result in the withholding of health services. The physician/investigator must assure them that their decision on whether to participate will not affect the therapeutic relationship or other benefits to which they are entitled. In this situation the ethical review committee should consider whether a neutral third party should seek informed consent. The prospective subject must not be exposed to undue influence. The borderline between justifiable persuasion and undue influence is imprecise, however. The researcher should give no unjustifiable assurances about the benefits, risks or inconveniences of the research, for example, or induce a close relative or a community leader to influence a prospective subject's decision. (See also Guideline 4: Individual informed consent.)

Risks. Investigators should be completely objective in discussing the details of the experimental intervention, the pain and discomfort that it may entail, and known risks and possible hazards. In complex research projects it may be neither feasible nor desirable to inform prospective participants fully about every possible risk. They must, however, be informed of all risks that a 'reasonable person' would consider material to making a decision about whether to participate, including risks to a spouse or partner associated with trials of, for example, psychotropic or genital-tract medicaments. (See also Guideline 8 Commentary, Risks to groups of persons.)

Exception to the requirement for informed consent in studies of emergency situations in which the researcher anticipates that many subjects will be unable to consent. Research protocols are sometimes designed to address conditions occurring suddenly and rendering the patients/subjects incapable of giving informed consent. Examples are head trauma, cardiopulmonary arrest and stroke. The investigation cannot be done with patients who can give informed consent in time and there may not be time to locate a person having the authority to give permission. In such circumstances it is often necessary to proceed with the research interventions very soon after the onset of the condition in order to evaluate an investigational treatment or develop the desired knowledge. As this class of emergency exception can be anticipated, the researcher must secure the review and approval of an ethical review committee before initiating the study. If possible, an attempt should be made to identify a population that is likely to develop the condition to be studied. This can be done readily, for example, if the condition is one that recurs periodically in individuals; examples include grand mal seizures and alcohol binges. In such cases, prospective subjects should be contacted while fully capable of informed consent, and invited to consent to their involvement as research subjects during future periods of incapacitation. If they are patients of an independent physician who is also the physician-researcher, the physician should likewise seek their consent while they are fully capable of informed consent. In all cases in which approved research has begun without prior consent of patients/subjects incapable of giving informed consent because of suddenly occurring conditions, they should be given all relevant information as soon as they are in a state to receive it, and their consent to continued participation should be obtained as soon as is reasonably

possible. Before proceeding without prior informed consent, the investigator must make reasonable efforts to locate an individual who has the authority to give permission on behalf of an incapacitated patient. If such a person can be located and refuses to give permission, the patient may not be enrolled as a subject. The risks of all interventions and procedures will be justified as required by Guideline 9 (Special limitations on risks when research involves individuals who are not capable of giving consent). The researcher and the ethical review committee should agree to a maximum time of involvement of an individual without obtaining either the individual's informed consent or authorization according to the applicable legal system if the person is not able to give consent. If by that time the researcher has not obtained either consent or permission—owing either to a failure to contact a representative or to a refusal of either the patient or the person or body authorized to give permission—the participation of the patient as a subject must be discontinued. The patient or the person or body providing authorization should be offered an opportunity to forbid the use of data derived from participation of the patient as a subject without consent or permission. Where appropriate, plans to conduct emergency research without prior consent of the subjects should be publicized within the community in which it will be carried out. In the design and conduct of the research, the ethical review committee, the investigators and the sponsors should be responsive to the concerns of the community. If there is cause for concern about the acceptability of the research in the community, there should be a formal consultation with representatives designated by the community. The research should not be carried out if it does not have substantial support in the community concerned. (See Guideline 8 Commentary, Risks to groups of persons.)

Exception to the requirement of informed consent for inclusion in clinical trials of persons rendered incapable of informed consent by an acute condition. Certain patients with an acute condition that renders them incapable of giving informed consent may be eligible for inclusion in a clinical trial in which the majority of prospective subjects will be capable of informed consent. Such a trial would relate to a new treatment for an acute condition such as sepsis, stroke or myocardial infarction. The investigational treatment would hold out the prospect of direct benefit and would be justified accordingly, though the investigation might involve certain procedures or interventions that were not of direct benefit but carried no more than minimal risk; an example would be the process of randomization or the collection of additional blood for research purposes. For such cases the initial protocol submitted for approval to the ethical review committee should anticipate that some patients may be incapable of consent, and should propose for such patients a form of proxy consent, such as permission of the responsible relative. When the ethical review committee has approved or cleared such a protocol, an investigator may seek the permission of the responsible relative and enrol such a patient.

Guideline 7: Inducement to participate

Subjects may be reimbursed for lost earnings, travel costs and other expenses incurred in taking part in a study; they may also receive free medical services. Subjects, particularly those who receive no direct benefit from research, may also be paid or otherwise compensated for inconvenience and time spent. The payments should not be so large, however, or the medical services so extensive as to induce prospective subjects to consent to participate in the research against their better judgment (“undue inducement”). All payments, reimbursements and medical services provided to research subjects must have been approved by an ethical review committee.

Commentary on Guideline 7:

Acceptable recompense. Research subjects may be reimbursed for their transport and other expenses, including lost earnings, associated with their participation in research. Those who receive no direct benefit from the research may also receive a small sum of money for inconvenience due to their participation in the research. All subjects may receive medical services unrelated to the research and have procedures and tests performed free of charge.

Unacceptable recompense. Payments in money or in kind to research subjects should not be so large as to persuade them to take undue risks or volunteer against their better judgment. Payments or rewards that undermine a person's capacity to exercise free choice invalidate consent. It may be difficult to distinguish between suitable recompense and undue influence to participate in research. An unemployed person or a student may view promised recompense differently from an employed person. Someone without access to medical care may or may not be unduly influenced to participate in research simply to receive such care. A prospective subject may be induced to participate in order to obtain a better diagnosis or access to a drug not otherwise available; local ethical review committees may find such inducements acceptable. Monetary and in-kind recompense must, therefore, be evaluated in the light of the traditions of the particular culture and population in which they are offered, to determine whether they constitute undue influence. The ethical review committee will ordinarily be the best judge of what constitutes reasonable material recompense in particular circumstances. When research interventions or procedures that do not hold out the prospect of direct benefit present more than minimal risk, all parties involved in the research—sponsors, investigators and ethical review committees—in both funding and host countries should be careful to avoid undue material inducement.

Incompetent persons. Incompetent persons may be vulnerable to exploitation for financial gain by guardians. A guardian asked to give permission on behalf of an incompetent person should be offered no recompense other than a refund of travel and related expenses.

Withdrawal from a study. A subject who withdraws from research for reasons related to the study, such as unacceptable side-effects of a study drug, or who is withdrawn on health grounds, should be paid or recompensed as if

full participation had taken place. A subject who withdraws for any other reason should be paid in proportion to the amount of participation. An investigator who must remove a subject from the study for wilful noncompliance is entitled to withhold part or all of the payment.

Guideline 8: Benefits and risks of study participation

For all biomedical research involving human subjects, the investigator must ensure that potential benefits and risks are reasonably balanced and risks are minimized. Interventions or procedures that hold out the prospect of direct diagnostic, therapeutic or preventive benefit for the individual subject must be justified by the expectation that they will be at least as advantageous to the individual subject, in the light of foreseeable risks and benefits, as any available alternative. Risks of such 'beneficial' interventions or procedures must be justified in relation to expected benefits to the individual subject. Risks of interventions that do not hold out the prospect of direct diagnostic, therapeutic or preventive benefit for the individual must be justified in relation to the expected benefits to society (generalizable knowledge). The risks presented by such interventions must be reasonable in relation to the importance of the knowledge to be gained.

Commentary on Guideline 8: The Declaration of Helsinki in several paragraphs deals with the well-being of research subjects and the avoidance of risk. Thus, considerations related to the well-being of the human subject should take precedence over the interests of science and society (Paragraph 5); clinical testing must be preceded by adequate laboratory or animal experimentation to demonstrate a reasonable probability of success without undue risk (Paragraph 11); every project should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others (Paragraph 16); physician-researchers must be confident that the risks involved have been adequately assessed and can be satisfactorily managed (Paragraph 17); and the risks and burdens to the subject must be minimized, and reasonable in relation to the importance of the objective or the knowledge to be gained (Paragraph 18). Biomedical research often employs a variety of interventions of which some hold out the prospect of direct therapeutic benefit (beneficial interventions) and others are administered solely to answer the research question (non-beneficial interventions). Beneficial interventions are justified as they are in medical practice by the expectation that they will be at least as advantageous to the individuals concerned, in the light of both risks and benefits, as any available alternative. Non-beneficial interventions are assessed differently; they may be justified only by appeal to the knowledge to be gained. In assessing the risks and benefits that a protocol presents to a population, it is appropriate to consider the harm that could result from forgoing the research. Paragraphs 5 and 18 of the Declaration of Helsinki do not preclude well-informed volunteers, capable of fully appreciating risks and benefits of an investigation, from participating in research for altruistic reasons or for modest remuneration.

Minimizing risk associated with participation in a randomized controlled trial. In randomized controlled trials subjects risk being allocated to receive the treatment that proves inferior. They are allocated by chance to one of two or more intervention arms and followed to a predetermined end-point. (Interventions are understood to include new or established therapies, diagnostic tests and preventive measures.) An intervention is evaluated by comparing it with another intervention (a control), which is ordinarily the best current method, selected from the safe and effective treatments available globally, unless some other control intervention such as placebo can be justified ethically (See Guideline 11). To minimize risk when the intervention to be tested in a randomized controlled trial is designed to prevent or postpone a lethal or disabling outcome, the investigator must not, for purposes of conducting the trial, withhold therapy that is known to be superior to the intervention being tested, unless the withholding can be justified by the standards set forth in Guideline 11. Also, the investigator must provide in the research protocol for the monitoring of research data by an independent board (Data and Safety Monitoring Board); one function of such a board is to protect the research subjects from previously unknown adverse reactions or unnecessarily prolonged exposure to an inferior therapy. Normally at the outset of a randomized controlled trial, criteria are established for its premature termination (stopping rules or guidelines).

Risks to groups of persons. Research in certain fields, such as epidemiology, genetics or sociology, may present risks to the interests of communities, societies, or racially or ethnically defined groups. Information might be published that could stigmatize a group or expose its members to discrimination. Such information, for example, could indicate, rightly or wrongly, that the group has a higher than average prevalence of alcoholism, mental illness or sexually transmitted disease, or is particularly susceptible to certain genetic disorders. Plans to conduct such research should be sensitive to such considerations, to the need to maintain confidentiality during and after the study, and to the need to publish the resulting data in a manner that is respectful of the interests of all concerned, or in certain circumstances not to publish them. The ethical review committee should ensure that the interests of all concerned are given due consideration; often it will be advisable to have individual consent supplemented by community consultation. [The ethical basis for the justification of risk is elaborated further in Guideline 9.]

Guideline 9: Special limitations on risk when research involves individuals who are not capable of giving informed consent

When there is ethical and scientific justification to conduct research with individuals incapable of giving informed consent, the risk from research interventions that do not hold out the prospect of direct benefit for the individual subject should be no more likely and not greater than the risk attached to routine medical or psychological examination of such persons. Slight or minor increases above such risk may be permitted when there is an overriding scien-

tific or medical rationale for such increases and when an ethical review committee has approved them.

Commentary on Guideline 9:

The low-risk standard. Certain individuals or groups may have limited capacity to give informed consent either because, as in the case of prisoners, their autonomy is limited, or because they have limited cognitive capacity. For research involving persons who are unable to consent, or whose capacity to make an informed choice may not fully meet the standard of informed consent, ethical review committees must distinguish between intervention risks that do not exceed those associated with routine medical or psychological examination of such persons and risks in excess of those. When the risks of such interventions do not exceed those associated with routine medical or psychological examination of such persons, there is no requirement for special substantive or procedural protective measures apart from those generally required for all research involving members of the particular class of persons. When the risks are in excess of those, the ethical review committee must find:

- (1) that the research is designed to be responsive to the disease affecting the prospective subjects or to conditions to which they are particularly susceptible;
- (2) that the risks of the research interventions are only slightly greater than those associated with routine medical or psychological examination of such persons for the condition or set of clinical circumstances under investigation;
- (3) that the objective of the research is sufficiently important to justify exposure of the subjects to the increased risk; and
- (4) that the interventions are reasonably commensurate with the clinical interventions that the subjects have experienced or may be expected to experience in relation to the condition under investigation.

If such research subjects, including children, become capable of giving independent informed consent during the research, their consent to continued participation should be obtained. There is no internationally agreed, precise definition of a “slight or minor increase” above the risks associated with routine medical or psychological examination of such persons. Its meaning is inferred from what various ethical review committees have reported as having met the standard. Examples include additional lumbar punctures or bone-marrow aspirations in children with conditions for which such examinations are regularly indicated in clinical practice. The requirement that the objective of the research be relevant to the disease or condition affecting the prospective subjects rules out the use of such interventions in healthy children. The requirement that the research interventions be reasonably commensurate with clinical interventions that subjects may have experienced or are likely to experience for the condition under investigation is intended to enable them to draw on personal experience as they decide whether to accept or reject additional procedures for research purposes. Their choices will, therefore, be more informed even though they may not fully meet the standard of informed consent. (See also Guidelines 4: Individual informed consent; 13: Research involving vulnerable persons; 14: Research involving children; and 15: Research involving individuals who by reason of mental or behavioural disorders are not capable of giving adequately informed consent.)

Guideline 10: Research in populations and communities with limited resources

Before undertaking research in a population or community with limited resources, the sponsor and the investigator must make every effort to ensure that:

- the research is responsive to the health needs and the priorities of the population or community in which it is to be carried out; and
- any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community.

Commentary on Guideline 10: This guideline is concerned with countries or communities in which resources are limited to the extent that they are, or may be, vulnerable to exploitation by sponsors and investigators from the relatively wealthy countries and communities.

Responsiveness of research to health needs and priorities. The ethical requirement that research be responsive to the health needs of the population or community in which it is carried out calls for decisions on what is needed to fulfil the requirement. It is not sufficient simply to determine that a disease is prevalent in the population and that new or further research is needed: the ethical requirement of “responsiveness” can be fulfilled only if successful interventions or other kinds of health benefit are made available to the population. This is applicable especially to research conducted in countries where governments lack the resources to make such products or benefits widely available. Even when a product to be tested in a particular country is much cheaper than the standard treatment in some other countries, the government or individuals in that country may still be unable to afford it. If the knowledge gained from the research in such a country is used primarily for the benefit of populations that can afford the tested product, the research may rightly be characterized as exploitative and, therefore, unethical. When an investigational intervention has important potential for health care in the host country, the negotiation that the sponsor should undertake to determine the practical implications of “responsiveness,” as well as “reasonable availability,” should

include representatives of stakeholders in the host country; these include the national government, the health ministry, local health authorities, and concerned scientific and ethics groups, as well as representatives of the communities from which subjects are drawn and non-governmental organizations such as health advocacy groups. The negotiation should cover the health-care infrastructure required for safe and rational use of the intervention, the likelihood of authorization for distribution, and decisions regarding payments, royalties, subsidies, technology and intellectual property, as well as distribution costs, when this economic information is not proprietary. In some cases, satisfactory discussion of the availability and distribution of successful products will necessarily engage international organizations, donor governments and bilateral agencies, international nongovernmental organizations, and the private sector. The development of a health-care infrastructure should be facilitated at the onset so that it can be of use during and beyond the conduct of the research. Additionally, if an investigational drug has been shown to be beneficial, the sponsor should continue to provide it to the subjects after the conclusion of the study, and pending its approval by a drug regulatory authority. The sponsor is unlikely to be in a position to make a beneficial investigational intervention generally available to the community or population until some time after the conclusion of the study, as it may be in short supply and in any case cannot be made generally available before a drug regulatory authority has approved it. For minor research studies and when the outcome is scientific knowledge rather than a commercial product, such complex planning or negotiation is rarely, if ever, needed. There must be assurance, however, that the scientific knowledge developed will be used for the benefit of the population.

Reasonable availability. The issue of “reasonable availability” is complex and will need to be determined on a case-by-case basis. Relevant considerations include the length of time for which the intervention or product developed, or other agreed benefit, will be made available to research subjects, or to the community or population concerned; the severity of a subject’s medical condition; the effect of withdrawing the study drug (e.g., death of a subject); the cost to the subject or health service; and the question of undue inducement if an intervention is provided free of charge. In general, if there is good reason to believe that a product developed or knowledge generated by research is unlikely to be reasonably available to, or applied to the benefit of, the population of a proposed host country or community after the conclusion of the research, it is unethical to conduct the research in that country or community. This should not be construed as precluding studies designed to evaluate novel therapeutic concepts. As a rare exception, for example, research may be designed to obtain preliminary evidence that a drug or a class of drugs has a beneficial effect in the treatment of a disease that occurs only in regions with extremely limited resources, and it could not be carried out reasonably well in more developed communities. Such research may be justified ethically even if there is no plan in place to make a product available to the population of the host country or community at the conclusion of the preliminary phase of its development. If the concept is found to be valid, subsequent phases of the research could result in a product that could be made reasonably available at its conclusion. (See also Guidelines 3: Ethical review of externally sponsored research; 12, Equitable distribution of burdens and benefits; 20: Strengthening capacity for ethical and scientific review and biomedical research; and 21: Ethical obligation of external sponsors to provide health-care services.)

Guideline 11: Choice of control in clinical trials

As a general rule, research subjects in the control group of a trial of a diagnostic, therapeutic, or preventive intervention should receive an established effective intervention. In some circumstances it may be ethically acceptable to use an alternative comparator, such as placebo or “no treatment.” Placebo may be used:

- when there is no established effective intervention;
- when withholding an established effective intervention would expose subjects to, at most, temporary discomfort or delay in relief of symptoms; and
- when use of an established effective intervention as comparator would not yield scientifically reliable results and use of placebo would not add any risk of serious or irreversible harm to the subjects.

Commentary on Guideline 11:

General considerations for controlled clinical trials. The design of trials of investigational diagnostic, therapeutic or preventive interventions raises interrelated scientific and ethical issues for sponsors, investigators and ethical review committees. To obtain reliable results, investigators must compare the effects of an investigational intervention on subjects assigned to the investigational arm (or arms) of a trial with the effects that a control intervention produces in subjects drawn from the same population and assigned to its control arm. Randomization is the preferred method for assigning subjects to the various arms of the clinical trial unless another method, such as historical or literature controls, can be justified scientifically and ethically. Assignment to treatment arms by randomization, in addition to its usual scientific superiority, offers the advantage of tending to render equivalent to all subjects the foreseeable benefits and risks of participation in a trial. A clinical trial cannot be justified ethically unless it is capable of producing scientifically reliable results. When the objective is to establish the effectiveness and safety of an investigational intervention, the use of a placebo control is often much more likely than that of an active control to produce a scientifically reliable result. In many cases the ability of a trial to distinguish effective from ineffective interventions (its assay sensitivity) cannot be assured unless the control is a placebo. If, however, an effect of using a placebo would

be to deprive subjects in the control arm of an established effective intervention, and thereby to expose them to serious harm, particularly if it is irreversible, it would obviously be unethical to use a placebo.

Placebo control in the absence of a current effective alternative. The use of placebo in the control arm of a clinical trial is ethically acceptable when, as stated in the Declaration of Helsinki (Paragraph 29), “no proven prophylactic, diagnostic or therapeutic method exists.” Usually, in this case, a placebo is scientifically preferable to no intervention. In certain circumstances, however, an alternative design may be both scientifically and ethically acceptable, and preferable; an example would be a clinical trial of a surgical intervention, because, for many surgical interventions, either it is not possible or it is ethically unacceptable to devise a suitable placebo; for another example, in certain vaccine trials an investigator might choose to provide for those in the ‘control’ arm a vaccine that is unrelated to the investigational vaccine.

Placebo-controlled trials that entail only minor risks. A placebo-controlled design may be ethically acceptable, and preferable on scientific grounds, when the condition for which patients/subjects are randomly assigned to placebo or active treatment is only a small deviation in physiological measurements, such as slightly raised blood pressure or a modest increase in serum cholesterol; and if delaying or omitting available treatment may cause only temporary discomfort (e.g., common headache) and no serious adverse consequences. The ethical review committee must be fully satisfied that the risks of withholding an established effective intervention are truly minor and short-lived.

Placebo control when active control would not yield reliable results. A related but distinct rationale for using a placebo control rather than an established effective intervention is that the documented experience with the established effective intervention is not sufficient to provide a scientifically reliable comparison with the intervention being investigated; it is then difficult, or even impossible, without using a placebo, to design a scientifically reliable study. This is not always, however, an ethically acceptable basis for depriving control subjects of an established effective intervention in clinical trials; only when doing so would not add any risk of serious harm, particularly irreversible harm, to the subjects would it be ethically acceptable to do so. In some cases, the condition at which the intervention is aimed (for example, cancer or HIV / AIDS) will be too serious to deprive control subjects of an established effective intervention. This latter rationale (when active control would not yield reliable results) differs from the former (trials that entail only minor risks) in emphasis. In trials that entail only minor risks the investigative interventions are aimed at relatively trivial conditions, such as the common cold or hair loss; forgoing an established effective intervention for the duration of a trial deprives control subjects of only minor benefits. It is for this reason that it is not unethical to use a placebo-control design. Even if it were possible to design a so-called “non-inferiority,” or “equivalency,” trial using an active control, it would still not be unethical in these circumstances to use a placebo-control design. In any event, the researcher must satisfy the ethical review committee that the safety and human rights of the subjects will be fully protected, that prospective subjects will be fully informed about alternative treatments, and that the purpose and design of the study are scientifically sound. The ethical acceptability of such placebo-controlled studies increases as the period of placebo use is decreased, and when the study design permits change to active treatment (“escape treatment”) if intolerable symptoms occur.

Exceptional use of a comparator other than an established effective intervention. An exception to the general rule is applicable in some studies designed to develop a therapeutic, preventive or diagnostic intervention for use in a country or community in which an established effective intervention is not available and unlikely in the foreseeable future to become available, usually for economic or logistic reasons. The purpose of such a study is to make available to the population of the country or community an effective alternative to an established effective intervention that is locally unavailable. Accordingly, the proposed investigational intervention must be responsive to the health needs of the population from which the research subjects are recruited and there must be assurance that, if it proves to be safe and effective, it will be made reasonably available to that population. Also, the scientific and ethical review committees must be satisfied that the established effective intervention cannot be used as comparator because its use would not yield scientifically reliable results that would be relevant to the health needs of the study population. In these circumstances an ethical review committee can approve a clinical trial in which the comparator is other than an established effective intervention, such as placebo or no treatment or a local remedy. However, some people strongly object to the exceptional use of a comparator other than an established effective intervention because it could result in exploitation of poor and disadvantaged populations. The objection rests on three arguments:

- (1) Placebo control could expose research subjects to risk of serious or irreversible harm when the use of an established effective intervention as comparator could avoid the risk.
- (2) Not all scientific experts agree about conditions under which an established effective intervention used as a comparator would not yield scientifically reliable results.
- (3) An economic reason for the unavailability of an established effective intervention cannot justify a placebo-controlled study in a country of limited resources when it would be unethical to conduct a study with the same design in a population with general access to the effective intervention outside the study.

Placebo control when an established effective intervention is not available in the host country. The question addressed here is: when should an exception be allowed to the general rule that subjects in the control arm of a

clinical trial should receive an established effective intervention? The usual reason for proposing the exception is that, for economic or logistic reasons, an established effective intervention is not in general use or available in the country in which the study will be conducted, whereas the investigational intervention could be made available, given the finances and infrastructure of the country. Another reason that may be advanced for proposing a placebo-controlled trial is that using an established effective intervention as the control would not produce scientifically reliable data relevant to the country in which the trial is to be conducted. Existing data about the effectiveness and safety of the established effective intervention may have been accumulated under circumstances unlike those of the population in which it is proposed to conduct the trial; this, it may be argued, could make their use in the trial unreliable. One reason could be that the disease or condition manifests itself differently in different populations, or other uncontrolled factors could invalidate the use of existing data for comparative purposes. The use of placebo control in these circumstances is ethically controversial, for the following reasons:

- Sponsors of research might use poor countries or communities as testing grounds for research that would be difficult or impossible in countries where there is general access to an established effective intervention, and the investigational intervention, if proven safe and effective, is likely to be marketed in countries in which an established effective intervention is already available and it is not likely to be marketed in the host country.
- The research subjects, both active-arm and control-arm, are patients who may have a serious, possibly life-threatening, illness. They do not normally have access to an established effective intervention currently available to similar patients in many other countries. According to the requirements of a scientifically reliable trial, investigators, who may be their attending physicians, would be expected to enrol some of those patients/subjects in the placebo-control arm. This would appear to be a violation of the physician's fiduciary duty of undivided loyalty to the patient, particularly in cases in which known effective therapy could be made available to the patients.
- An argument for exceptional use of placebo control may be that a health authority in a country where an established effective intervention is not generally available or affordable, and unlikely to become available or affordable in the foreseeable future, seeks to develop an affordable intervention specifically for a health problem affecting its population. There may then be less reason for concern that a placebo design is exploitative, and therefore unethical, as the health authority has responsibility for the population's health, and there are valid health grounds for testing an apparently beneficial intervention. In such circumstances an ethical review committee may determine that the proposed trial is ethically acceptable, provided that the rights and safety of subjects are safeguarded.

Ethical review committees will need to engage in careful analysis of the circumstances to determine whether the use of placebo rather than an established effective intervention is ethically acceptable. They will need to be satisfied that an established effective intervention is truly unlikely to become available and implementable in that country. This may be difficult to determine, however, as it is clear that, with sufficient persistence and ingenuity, ways may be found of accessing previously unattainable medicinal products, and thus avoiding the ethical issue raised by the use of placebo control. When the rationale of proposing a placebo-controlled trial is that the use of an established effective intervention as the control would not yield scientifically reliable data relevant to the proposed host country, the ethical review committee in that country has the option of seeking expert opinion as to whether use of an established effective intervention in the control arm would invalidate the results of the research.

An "equivalency trial" as an alternative to a placebo-controlled trial. An alternative to a placebo-control design in these circumstances would be an "equivalency trial," which would compare an investigational intervention with an established effective intervention and produce scientifically reliable data. An equivalency trial in a country in which no established effective intervention is available is not designed to determine whether the investigational intervention is superior to an established effective intervention currently used somewhere in the world; its purpose is, rather, to determine whether the investigational intervention is, in effectiveness and safety, equivalent to, or almost equivalent to, the established effective intervention. It would be hazardous to conclude, however, that an intervention demonstrated to be equivalent, or almost equivalent, to an established effective intervention is better than nothing or superior to whatever intervention is available in the country; there may be substantial differences between the results of superficially identical clinical trials carried out in different countries. If there are such differences, it would be scientifically acceptable and ethically preferable to conduct such 'equivalency' trials in countries in which an established effective intervention is already available. If there are substantial grounds for the ethical review committee to conclude that an established effective intervention will not become available and implementable, the committee should obtain assurances from the parties concerned that plans have been agreed for making the investigational intervention reasonably available in the host country or community once its effectiveness and safety have been established. Moreover, when the study has external sponsorship, approval should usually be dependent on the sponsors and the health authorities of the host country having engaged in a process of negotiation and planning, including justifying the study in regard to local health-care needs.

Means of minimizing harm to placebo-control subjects. Even when placebo controls are justified on one of the

bases set forth in the guideline, there are means of minimizing the possibly harmful effect of being in the control arm. First, a placebo-control group need not be untreated. An add-on design may be employed when the investigational therapy and a standard treatment have different mechanisms of action. The treatment to be tested and placebo are each added to a standard treatment. Such studies have a particular place when a standard treatment is known to decrease mortality or irreversible morbidity but a trial with standard treatment as the active control cannot be carried out or would be difficult to interpret [International Conference on Harmonisation (ICH) Guideline: Choice of Control Group and Related Issues in Clinical Trials, 2000]. In testing for improved treatment of life-threatening diseases such as cancer, HIV/AIDS, or heart failure, add-on designs are a particularly useful means of finding improvements in interventions that are not fully effective or may cause intolerable side-effects. They have a place also in respect of treatment for epilepsy, rheumatism and osteoporosis, for example, because withholding of established effective therapy could result in progressive disability, unacceptable discomfort or both. Second, as indicated in Guideline 8 Commentary, when the intervention to be tested in a randomized controlled trial is designed to prevent or postpone a lethal or disabling outcome, the investigator minimizes harmful effects of placebo-control studies by providing in the research protocol for the monitoring of research data by an independent Data and Safety Monitoring Board (DSMB). One function of such a board is to protect the research subjects from previously unknown adverse reactions; another is to avoid unnecessarily prolonged exposure to an inferior therapy. The board fulfils the latter function by means of interim analyses of the data pertaining to efficacy to ensure that the trial does not continue beyond the point at which an investigational therapy is demonstrated to be effective. Normally, at the outset of a randomized controlled trial, criteria are established for its premature termination (stopping rules or guidelines). In some cases the DSMB is called upon to perform "conditional power calculations," designed to determine the probability that a particular clinical trial could ever show that the investigational therapy is effective. If that probability is very small, the DSMB is expected to recommend termination of the clinical trial, because it would be unethical to continue it beyond that point. In most cases of research involving human subjects, it is unnecessary to appoint a DSMB. To ensure that research is carefully monitored for the early detection of adverse events, the sponsor or the principal investigator appoints an individual to be responsible for advising on the need to consider changing the system of monitoring for adverse events or the process of informed consent, or even to consider terminating the study.

Guideline 12: Equitable distribution of burdens and benefits in the selection of groups of subjects in research

Groups or communities to be invited to be subjects of research should be selected in such a way that the burdens and benefits of the research will be equitably distributed. The exclusion of groups or communities that might benefit from study participation must be justified.

Commentary on Guideline 12:

General considerations. Equity requires that no group or class of persons should bear more than its fair share of the burdens of participation in research. Similarly, no group should be deprived of its fair share of the benefits of research, short-term or long-term; such benefits include the direct benefits of participation as well as the benefits of the new knowledge that the research is designed to yield. When burdens or benefits of research are to be apportioned unequally among individuals or groups of persons, the criteria for unequal distribution should be morally justifiable and not arbitrary. In other words, unequal allocation must not be inequitable. Subjects should be drawn from the qualifying population in the general geographic area of the trial without regard to race, ethnicity, economic status or gender unless there is a sound scientific reason to do otherwise. In the past, groups of persons were excluded from participation in research for what were then considered good reasons. As a consequence of such exclusions, information about the diagnosis, prevention and treatment of diseases in such groups of persons is limited. This has resulted in a serious class injustice. If information about the management of diseases is considered a benefit that is distributed within a society, it is unjust to deprive groups of persons of that benefit. Such documents as the Declaration of Helsinki and the UNAIDS Guidance Document Ethical Considerations in HIV Preventive Vaccine Research, and the policies of many national governments and professional societies, recognize the need to redress these injustices by encouraging the participation of previously excluded groups in basic and applied biomedical research. Members of vulnerable groups also have the same entitlement to access to the benefits of investigational interventions that show promise of therapeutic benefit as persons not considered vulnerable, particularly when no superior or equivalent approaches to therapy are available. There has been a perception, sometimes correct and sometimes incorrect, that certain groups of persons have been overused as research subjects. In some cases such overuse has been based on the administrative availability of the populations. Research hospitals are often located in places where members of the lowest socioeconomic classes reside, and this has resulted in an apparent overuse of such persons. Other groups that may have been overused because they were conveniently available to researchers include students in investigators' classes, residents of long-term care facilities and subordinate members of hierarchical institutions. Impoverished groups have been overused because of their willingness to serve as subjects in exchange for relatively small stipends. Prisoners have been considered ideal subjects for Phase I drug studies because of their highly regimented lives and, in many cases, their conditions of economic deprivation. Overuse of certain groups, such as the poor or the administratively available, is unjust for several reasons. It is unjust to selectively recruit impoverished people to serve as research subjects simply because they can be more easily induced to participate in exchange for small payments. In most

cases, these people would be called upon to bear the burdens of research so that others who are better off could enjoy the benefits. However, although the burdens of research should not fall disproportionately on socio-economically disadvantaged groups, neither should such groups be categorically excluded from research protocols. It would not be unjust to selectively recruit poor people to serve as subjects in research designed to address problems that are prevalent in their group—malnutrition, for example. Similar considerations apply to institutionalized groups or those whose availability to the investigators is for other reasons administratively convenient. Not only may certain groups within a society be inappropriately overused as research subjects, but also entire communities or societies may be overused. This has been particularly likely to occur in countries or communities with insufficiently well-developed systems for the protection of the rights and welfare of human research subjects. Such overuse is especially questionable when the populations or communities concerned bear the burdens of participation in research but are extremely unlikely ever to enjoy the benefits of new knowledge and products developed as a result of the research. (See Guideline 10: Research in populations and communities with limited resources.)

Guideline 13: Research involving vulnerable persons

Special justification is required for inviting vulnerable individuals to serve as research subjects and, if they are selected, the means of protecting their rights and welfare must be strictly applied.

Commentary on Guideline 13: Vulnerable persons are those who are relatively (or absolutely) incapable of protecting their own interests. More formally, they may have insufficient power, intelligence, education, resources, strength, or other needed attributes to protect their own interests.

General considerations. The central problem presented by plans to involve vulnerable persons as research subjects is that such plans may entail an inequitable distribution of the burdens and benefits of research participation. Classes of individuals conventionally considered vulnerable are those with limited capacity or freedom to consent or to decline to consent. They are the subject of specific guidelines in this document (Guidelines 14, 15) and include children, and persons who because of mental or behavioural disorders are incapable of giving informed consent. Ethical justification of their involvement usually requires that investigators satisfy ethical review committees that:

- the research could not be carried out equally well with less vulnerable subjects;
- the research is intended to obtain knowledge that will lead to improved diagnosis, prevention or treatment of diseases or other health problems characteristic of, or unique to, the vulnerable class— either the actual subjects or other similarly situated members of the vulnerable class;
- research subjects and other members of the vulnerable class from which subjects are recruited will ordinarily be assured reasonable access to any diagnostic, preventive or therapeutic products that will become available as a consequence of the research;
- the risks attached to interventions or procedures that do not hold out the prospect of direct health-related benefit will not exceed those associated with routine medical or psychological examination of such persons unless an ethical review committee authorizes a slight increase over this level of risk (Guideline 9); and
- when the prospective subjects are either incompetent or otherwise substantially unable to give informed consent, their agreement will be supplemented by the permission of their legal guardians or other appropriate representatives.

Other vulnerable groups. The quality of the consent of prospective subjects who are junior or subordinate members of a hierarchical group requires careful consideration, as their agreement to volunteer may be unduly influenced, whether justified or not, by the expectation of preferential treatment if they agree or by fear of disapproval or retaliation if they refuse. Examples of such groups are medical and nursing students, subordinate hospital and laboratory personnel, employees of pharmaceutical companies, and members of the armed forces or police. Because they work in close proximity to investigators, they tend to be called upon more often than others to serve as research subjects, and this could result in inequitable distribution of the burdens and benefits of research. Elderly persons are commonly regarded as vulnerable. With advancing age, people are increasingly likely to acquire attributes that define them as vulnerable. They may, for example, be institutionalized or develop varying degrees of dementia. If and when they acquire such vulnerability-defining attributes, and not before, it is appropriate to consider them vulnerable and to treat them accordingly. Other groups or classes may also be considered vulnerable. They include residents of nursing homes, people receiving welfare benefits or social assistance and other poor people and the unemployed, patients in emergency rooms, some ethnic and racial minority groups, homeless persons, nomads, refugees or displaced persons, prisoners, patients with incurable disease, individuals who are politically powerless, and members of communities unfamiliar with modern medical concepts. To the extent that these and other classes of people have attributes resembling those of classes identified as vulnerable, the need for special protection of their rights and welfare should be reviewed and applied, where relevant. Persons who have serious, potentially disabling or life-threatening diseases are highly vulnerable. Physicians sometimes treat such patients with drugs or other therapies not yet licensed for general availability because studies designed to establish their safety and efficacy have not been completed. This is compatible with the Declaration of Helsinki, which states in Paragraph 32: "In the treatment of a patient, where proven...therapeutic methods do not exist or have been ineffective, the physician, with informed

consent from the patient, must be free to use unproven or new...therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering." Such treatment, commonly called 'compassionate use,' is not properly regarded as research, but it can contribute to ongoing research into the safety and efficacy of the interventions used. Although, on the whole, investigators must study less vulnerable groups before involving more vulnerable groups, some exceptions are justified. In general, children are not suitable for Phase I drug trials or for Phase I or II vaccine trials, but such trials may be permissible after studies in adults have shown some therapeutic or preventive effect. For example, a Phase II vaccine trial seeking evidence of immunogenicity in infants may be justified when a vaccine has shown evidence of preventing or slowing progression of an infectious disease in adults, or Phase I research with children may be appropriate because the disease to be treated does not occur in adults or is manifested differently in children (Appendix 3: The phases of clinical trials of vaccines and drugs).

Guideline 14: Research involving children

Before undertaking research involving children, the investigator must ensure that:

- the research might not equally well be carried out with adults;
- the purpose of the research is to obtain knowledge relevant to the health needs of children;
- a parent or legal representative of each child has given permission;
- the agreement (assent) of each child has been obtained to the extent of the child's capabilities; and
- a child's refusal to participate or continue in the research will be respected.

Commentary on Guideline 14:

Justification of the involvement of children in biomedical research. The participation of children is indispensable for research into diseases of childhood and conditions to which children are particularly susceptible (cf. vaccine trials), as well as for clinical trials of drugs that are designed for children as well as adults. In the past, many new products were not tested for children though they were directed towards diseases also occurring in childhood; thus children either did not benefit from these new drugs or were exposed to them though little was known about their specific effects or safety in children. Now it is widely agreed that, as a general rule, the sponsor of any new therapeutic, diagnostic or preventive product that is likely to be indicated for use in children is obliged to evaluate its safety and efficacy for children before it is released for general distribution.

Assent of the child. The willing cooperation of the child should be sought, after the child has been informed to the extent that the child's maturity and intelligence permit. The age at which a child becomes legally competent to give consent differs substantially from one jurisdiction to another; in some countries the "age of consent" established in their different provinces, states or other political subdivisions varies considerably. Often children who have not yet reached the legally established age of consent can understand the implications of informed consent and go through the necessary procedures; they can therefore knowingly agree to serve as research subjects. Such knowing agreement, sometimes referred to as assent, is insufficient to permit participation in research unless it is supplemented by the permission of a parent, a legal guardian or other duly authorized representative. Some children who are too immature to be able to give knowing agreement, or assent, may be able to register a 'deliberate objection,' an expression of disapproval or refusal of a proposed procedure. The deliberate objection of an older child, for example, is to be distinguished from the behaviour of an infant, who is likely to cry or withdraw in response to almost any stimulus. Older children, who are more capable of giving assent, should be selected before younger children or infants, unless there are valid scientific reasons related to age for involving younger children first. A deliberate objection by a child to taking part in research should always be respected even if the parents have given permission, unless the child needs treatment that is not available outside the context of research, the investigational intervention shows promise of therapeutic benefit, and there is no acceptable alternative therapy. In such a case, particularly if the child is very young or immature, a parent or guardian may override the child's objections. If the child is older and more nearly capable of independent informed consent, the investigator should seek the specific approval or clearance of the scientific and ethical review committees for initiating or continuing with the investigational treatment. If child subjects become capable of independent informed consent during the research, their informed consent to continued participation should be sought and their decision respected. A child with a likely fatal illness may object or refuse assent to continuation of a burdensome or distressing intervention. In such circumstances parents may press an investigator to persist with an investigational intervention against the child's wishes. The investigator may agree to do so if the intervention shows promise of preserving or prolonging life and there is no acceptable alternative treatment. In such cases, the investigator should seek the specific approval or clearance of the ethical review committee before agreeing to override the wishes of the child.

Permission of a parent or guardian. The investigator must obtain the permission of a parent or guardian in accordance with local laws or established procedures. It may be assumed that children over the age of 12 or 13 years are usually capable of understanding what is necessary to give adequately informed consent, but their consent (assent) should normally be complemented by the permission of a parent or guardian, even when local law does not require such permission. Even when the law requires parental permission, however, the assent of the child must be obtained.

In some jurisdictions, some individuals who are below the general age of consent are regarded as “emancipated” or “mature” minors and are authorized to consent without the agreement or even the awareness of their parents or guardians. They may be married or pregnant or be already parents or living independently. Some studies involve investigation of adolescents’ beliefs and behaviour regarding sexuality or use of recreational drugs; other research addresses domestic violence or child abuse. For studies on these topics, ethical review committees may waive parental permission if, for example, parental knowledge of the subject matter may place the adolescents at some risk of questioning or even intimidation by their parents. Because of the issues inherent in obtaining assent from children in institutions, such children should only exceptionally be subjects of research. In the case of institutionalized children without parents, or whose parents are not legally authorized to grant permission, the ethical review committee may require sponsors or investigators to provide it with the opinion of an independent, concerned, expert advocate for institutionalized children as to the propriety of undertaking the research with such children.

Observation of research by a parent or guardian. A parent or guardian who gives permission for a child to participate in research should be given the opportunity, to a reasonable extent, to observe the research as it proceeds, so as to be able to withdraw the child if the parent or guardian decides it is in the child’s best interests to do so.

Psychological and medical support. Research involving children should be conducted in settings in which the child and the parent can obtain adequate medical and psychological support. As an additional protection for children, an investigator may, when possible, obtain the advice of a child’s family physician, paediatrician or other health-care provider on matters concerning the child’s participation in the research.

(See also Guideline 8: Benefits and risks of study participation; Guideline 9: Special limitations on risks when subjects are not capable of giving consent; and Guideline 13: Research involving vulnerable persons.)

Guideline 15: Research involving individuals who by reason of mental or behavioural disorders are not capable of giving adequately informed consent

Before undertaking research involving individuals who by reason of mental or behavioural disorders are not capable of giving adequately informed consent, the investigator must ensure that:

- such persons will not be subjects of research that might equally well be carried out on persons whose capacity to give adequately informed consent is not impaired;
- the purpose of the research is to obtain knowledge relevant to the particular health needs of persons with mental or behavioural disorders;
- the consent of each subject has been obtained to the extent of that person’s capabilities, and a prospective subject’s refusal to participate in research is always respected, unless, in exceptional circumstances, there is no reasonable medical alternative and local law permits overriding the objection; and
- in cases where prospective subjects lack capacity to consent, permission is obtained from a responsible family member or a legally authorized representative in accordance with applicable law.

Commentary on Guideline 15:

General considerations. Most individuals with mental or behavioural disorders are capable of giving informed consent; this Guideline is concerned only with those who are not capable or who because their condition deteriorates become temporarily incapable. They should never be subjects of research that might equally well be carried out on persons in full possession of their mental faculties, but they are clearly the only subjects suitable for a large part of research into the origins and treatment of certain severe mental or behavioural disorders.

Consent of the individual. The investigator must obtain the approval of an ethical review committee to include in research persons who by reason of mental or behavioural disorders are not capable of giving informed consent. The willing cooperation of such persons should be sought to the extent that their mental state permits, and any objection on their part to taking part in any study that has no components designed to benefit them directly should always be respected. The objection of such an individual to an investigational intervention intended to be of therapeutic benefit should be respected unless there is no reasonable medical alternative and local law permits overriding the objection. The agreement of an immediate family member or other person with a close personal relationship with the individual should be sought, but it should be recognized that these proxies may have their own interests that may call their permission into question. Some relatives may not be primarily concerned with protecting the rights and welfare of the patients. Moreover, a close family member or friend may wish to take advantage of a research study in the hope that it will succeed in “curing” the condition. Some jurisdictions do not permit third-party permission for subjects lacking capacity to consent. Legal authorization may be necessary to involve in research an individual who has been committed to an institution by a court order. Serious illness in persons who because of mental or behavioural disorders are unable to give adequately informed consent. Persons who because of mental or behavioural disorders are unable to give adequately informed consent and who have, or are at risk of, serious illnesses such as HIV infection, cancer or hepatitis should not be deprived of the possible benefits of investigational drugs, vaccines or devices that show promise of therapeutic or preventive benefit, particularly when no superior or equivalent therapy or prevention is available. Their entitlement to access to such therapy or prevention is justified ethically on the same grounds as is such entitlement for other vulnerable groups. Persons who are unable to give adequately informed consent by

reason of mental or behavioural disorders are, in general, not suitable for participation in formal clinical trials except those trials that are designed to be responsive to their particular health needs and can be carried out only with them.

(See also Guidelines 8: Benefits and risks of study participation; 9: Special limitations on risks when subjects are not capable of giving consent; and 13: Research involving vulnerable persons.)

Guideline 16: Women as research subjects

Investigators, sponsors or ethical review committees should not exclude women of reproductive age from biomedical research. The potential for becoming pregnant during a study should not, in itself, be used as a reason for precluding or limiting participation. However, a thorough discussion of risks to the pregnant woman and to her fetus is a prerequisite for the woman's ability to make a rational decision to enrol in a clinical study. In this discussion, if participation in the research might be hazardous to a fetus or a woman if she becomes pregnant, the sponsors/investigators should guarantee the prospective subject a pregnancy test and access to effective contraceptive methods before the research commences. Where such access is not possible, for legal or religious reasons, investigators should not recruit for such possibly hazardous research women who might become pregnant.

Commentary on Guideline 16: Women in most societies have been discriminated against with regard to their involvement in research. Women who are biologically capable of becoming pregnant have been customarily excluded from formal clinical trials of drugs, vaccines and medical devices owing to concern about undetermined risks to the fetus. Consequently, relatively little is known about the safety and efficacy of most drugs, vaccines or devices for such women, and this lack of knowledge can be dangerous. A general policy of excluding from such clinical trials women biologically capable of becoming pregnant is unjust in that it deprives women as a class of persons of the benefits of the new knowledge derived from the trials. Further, it is an affront to their right of self-determination. Nevertheless, although women of childbearing age should be given the opportunity to participate in research, they should be helped to understand that the research could include risks to the fetus if they become pregnant during the research. Although this general presumption favours the inclusion of women in research, it must be acknowledged that in some parts of the world women are vulnerable to neglect or harm in research because of their social conditioning to submit to authority, to ask no questions, and to tolerate pain and suffering. When women in such situations are potential subjects in research, investigators need to exercise special care in the informed consent process to ensure that they have adequate time and a proper environment in which to take decisions on the basis of clearly given information.

Individual consent of women. In research involving women of reproductive age, whether pregnant or non-pregnant, only the informed consent of the woman herself is required for her participation. In no case should the permission of a spouse or partner replace the requirement of individual informed consent. If women wish to consult with their husbands or partners or seek voluntarily to obtain their permission before deciding to enrol in research, that is not only ethically permissible but in some contexts highly desirable. A strict requirement of authorization of spouse or partner, however, violates the substantive principle of respect for persons. A thorough discussion of risks to the pregnant woman and to her fetus is a prerequisite for the woman's ability to make a rational decision to enrol in a clinical study. For women who are not pregnant at the outset of a study but who might become pregnant while they are still subjects, the consent discussion should include information about the alternative of voluntarily withdrawing from the study and, where legally permissible, terminating the pregnancy. Also, if the pregnancy is not terminated, they should be guaranteed a medical follow-up.

Guideline 17: Pregnant women as research participants.

Pregnant women should be presumed to be eligible for participation in biomedical research. Investigators and ethical review committees should ensure that prospective subjects who are pregnant are adequately informed about the risks and benefits to themselves, their pregnancies, the fetus and their subsequent offspring, and to their fertility. Research in this population should be performed only if it is relevant to the particular health needs of a pregnant woman or her fetus, or to the health needs of pregnant women in general, and, when appropriate, if it is supported by reliable evidence from animal experiments, particularly as to risks of teratogenicity and mutagenicity.

Commentary on Guideline 17: The justification of research involving pregnant women is complicated by the fact that it may present risks and potential benefits to two beings—the woman and the fetus—as well as to the person the fetus is destined to become. Though the decision about acceptability of risk should be made by the mother as part of the informed consent process, it is desirable in research directed at the health of the fetus to obtain the father's opinion also, when possible. Even when evidence concerning risks is unknown or ambiguous, the decision about acceptability of risk to the fetus should be made by the woman as part of the informed consent process. Especially in communities or societies in which cultural beliefs accord more importance to the fetus than to the woman's life or health, women may feel constrained to participate, or not to participate, in research. Special safeguards should be established to prevent undue inducement to pregnant women to participate in research in which interventions hold out the prospect of direct benefit to the fetus. Where fetal abnormality is not recognized as an indication for abortion, pregnant women should not be recruited for research in which there is a realistic basis for concern that fetal abnormality may occur as a consequence of participation as a subject in research. Investigators should include in protocols on research on pregnant women a plan for monitoring the outcome of the pregnancy with regard to both the health of the woman and the short-term and long-term health of the child.

Guideline 18: Safeguarding confidentiality

The investigator must establish secure safeguards of the confidentiality of subjects' research data. Subjects should be told the limits, legal or other, to the investigators' ability to safeguard confidentiality and the possible consequences of breaches of confidentiality.

Commentary on Guideline 18:

Confidentiality between investigator and subject. Research relating to individuals and groups may involve the collection and storage of information that, if disclosed to third parties, could cause harm or distress. Investigators should arrange to protect the confidentiality of such information by, for example, omitting information that might lead to the identification of individual subjects, limiting access to the information, anonymizing data, or other means. During the process of obtaining informed consent the investigator should inform the prospective subjects about the precautions that will be taken to protect confidentiality. Prospective subjects should be informed of limits to the ability of investigators to ensure strict confidentiality and of the foreseeable adverse social consequences of breaches of confidentiality. Some jurisdictions require the reporting to appropriate agencies of, for instance, certain communicable diseases or evidence of child abuse or neglect. Drug regulatory authorities have the right to inspect clinical-trial records, and a sponsor's clinical-compliance audit staff may require and obtain access to confidential data. These and similar limits to the ability to maintain confidentiality should be anticipated and disclosed to prospective subjects. Participation in HIV/AIDS drug and vaccine trials may impose upon the research subjects significant associated risks of social discrimination or harm; such risks merit consideration equal to that given to adverse medical consequences of the drugs and vaccines. Efforts must be made to reduce their likelihood and severity. For example, subjects in vaccine trials must be enabled to demonstrate that their HIV seropositivity is due to their having been vaccinated rather than to natural infection. This may be accomplished by providing them with documents attesting to their participation in vaccine trials, or by maintaining a confidential register of trial subjects, from which information can be made available to outside agencies at a subject's request.

Confidentiality between physician and patient. Patients have the right to expect that their physicians and other health-care professionals will hold all information about them in strict confidence and disclose it only to those who need, or have a legal right to, the information, such as other attending physicians, nurses, or other health-care workers who perform tasks related to the diagnosis and treatment of patients. A treating physician should not disclose any identifying information about patients to an investigator unless each patient has given consent to such disclosure and unless an ethical review committee has approved such disclosure. Physicians and other health care professionals record the details of their observations and interventions in medical and other records. Epidemiological studies often make use of such records. For such studies it is usually impracticable to obtain the informed consent of each identifiable patient; an ethical review committee may waive the requirement for informed consent when this is consistent with the requirements of applicable law and provided that there are secure safeguards of confidentiality. (See also Guideline 4 Commentary: Waiver of the consent requirement.) In institutions in which records may be used for research purposes without the informed consent of patients, it is advisable to notify patients generally of such practices; notification is usually by means of a statement in patient-information brochures. For research limited to patients' medical records, access must be approved or cleared by an ethical review committee and must be supervised by a person who is fully aware of the confidentiality requirements.

Issues of confidentiality in genetic research. An investigator who proposes to perform genetic tests of known clinical or predictive value on biological samples that can be linked to an identifiable individual must obtain the informed consent of the individual or, when indicated, the permission of a legally authorized representative. Conversely, before performing a genetic test that is of known predictive value or gives reliable information about a known heritable condition, and individual consent or permission has not been obtained, investigators must see that biological samples are fully anonymized and unlinked; this ensures that no information about specific individuals can be derived from such research or passed back to them. When biological samples are not fully anonymized and when it is anticipated that there may be valid clinical or research reasons for linking the results of genetic tests to research subjects, the investigator in seeking informed consent should assure prospective subjects that their identity will be protected by secure coding of their samples (encryption) and by restricted access to the database, and explain to them this process. When it is clear that for medical or possibly research reasons the results of genetic tests will be reported to the subject or to the subject's physician, the subject should be informed that such disclosure will occur and that the samples to be tested will be clearly labelled. Investigators should not disclose results of diagnostic genetic tests to relatives of subjects without the subjects' consent. In places where immediate family relatives would usually expect to be informed of such results, the research protocol, as approved or cleared by the ethical review committee, should indicate the precautions in place to prevent such disclosure of results without the subjects' consent; such plans should be clearly explained during the process of obtaining informed consent.

Guideline 19: Right of injured subjects to treatment and compensation

Investigators should ensure that research subjects who suffer injury as a result of their participation are entitled to free medical treatment for such injury and to such financial or other assistance as would compensate them equitably for any resultant impairment, disability or handicap. In the case of death as a result of their participation, their dependants are entitled to compensation. Subjects must not be asked to waive the right to compensation.

Commentary on Guideline 19:

Guideline 19 is concerned with two distinct but closely related entitlements. The first is the uncontroversial entitlement to free medical treatment and compensation for accidental injury inflicted by procedures or interventions performed exclusively to accomplish the purposes of research (non-therapeutic procedures). The second is the entitlement of dependants to material compensation for death or disability occurring as a direct result of study participation. Implementing a compensation system for research-related injuries or death is likely to be complex, however.

Equitable compensation and free medical treatment. Compensation is owed to research subjects who are disabled as a consequence of injury from procedures performed solely to accomplish the purposes of research. Compensation and free medical treatment are generally not owed to research subjects who suffer expected or foreseen adverse reactions to investigational therapeutic, diagnostic or preventive interventions when such reactions are not different in kind from those known to be associated with established interventions in standard medical practice. In the early stages of drug testing (Phase I and early Phase II), it is generally unreasonable to assume that an investigational drug holds out the prospect of direct benefit for the individual subject; accordingly, compensation is usually owed to individuals who become disabled as a result of serving as subjects in such studies. The ethical review committee should determine in advance:

- (i) the injuries for which subjects will receive free treatment and, in case of impairment, disability or handicap resulting from such injuries, be compensated; and
- (ii) the injuries for which they will not be compensated.

Prospective subjects should be informed of the committee's decisions, as part of the process of informed consent. As an ethical review committee cannot make such advance determination in respect of unexpected or unforeseen adverse reactions, such reactions must be presumed compensable and should be reported to the committee for prompt review as they occur. Subjects must not be asked to waive their rights to compensation or required to show negligence or lack of a reasonable degree of skill on the part of the investigator in order to claim free medical treatment or compensation. The informed consent process or form should contain no words that would absolve an investigator from responsibility in the case of accidental injury, or that would imply that subjects would waive their right to seek compensation for impairment, disability or handicap. Prospective subjects should be informed that they will not need to take legal action to secure the free medical treatment or compensation for injury to which they may be entitled. They should also be told what medical service or organization or individual will provide the medical treatment and what organization will be responsible for providing compensation.

Obligation of the sponsor with regard to compensation. Before the research begins, the sponsor, whether a pharmaceutical company or other organization or institution, or a government (where government insurance is not precluded by law), should agree to provide compensation for any physical injury for which subjects are entitled to compensation, or come to an agreement with the investigator concerning the circumstances in which the investigator must rely on his or her own insurance coverage (for example, for negligence or failure of the investigator to follow the protocol, or where government insurance coverage is limited to negligence). In certain circumstances it may be advisable to follow both courses. Sponsors should seek adequate insurance against risks to cover compensation, independent of proof of fault.

Guideline 20: Strengthening capacity for ethical and scientific review and biomedical research

Many countries lack the capacity to assess or ensure the scientific quality or ethical acceptability of biomedical research proposed or carried out in their jurisdictions. In externally sponsored collaborative research, sponsors and investigators have an ethical obligation to ensure that biomedical research projects for which they are responsible in such countries contribute effectively to national or local capacity to design and conduct biomedical research, and to provide scientific and ethical review and monitoring of such research. Capacity-building may include, but is not limited to, the following activities:

- establishing and strengthening independent and competent ethical review processes/ committees
- strengthening research capacity
- developing technologies appropriate to health-care and biomedical research
- training of research and health-care staff
- educating the community from which research subjects will be drawn

Commentary on Guideline 20: External sponsors and investigators have an ethical obligation to contribute to a host country's sustainable capacity for independent scientific and ethical review and biomedical research. Before undertaking research in a host country with little or no such capacity, external sponsors and investigators should include in the research protocol a plan that specifies the contribution they will make. The amount of capacity building reasonably expected should be proportional to the magnitude of the research project. A brief epidemiological study involving only review of medical records, for example, would entail relatively little, if any, such development, whereas a considerable contribution is to be expected of an external sponsor of, for instance, a large-scale vaccine

field-trial expected to last two or three years. The specific capacity-building objectives should be determined and achieved through dialogue and negotiation between external sponsors and host-country authorities. External sponsors would be expected to employ and, if necessary, train local individuals to function as investigators, research assistants or data managers, for example, and to provide, as necessary, reasonable amounts of financial, educational and other assistance for capacity-building. To avoid conflict of interest and safeguard the independence of review committees, financial assistance should not be provided directly to them; rather, funds should be made available to appropriate authorities in the host-country government or to the host research institution. (See also Guideline 10: Research in populations and communities with limited resources.)

Guideline 21: Ethical obligation of external sponsors to provide health-care services

External sponsors are ethically obliged to ensure the availability of:

- health-care services that are essential to the safe conduct of the research;
- treatment for subjects who suffer injury as a consequence of research interventions; and
- services that are a necessary part of the commitment of a sponsor to make a beneficial intervention or product developed as a result of the research reasonably available to the population or community concerned.

Commentary on Guideline 21:

Obligations of external sponsors to provide health-care services will vary with the circumstances of particular studies and the needs of host countries. The sponsors' obligations in particular studies should be clarified before the research is begun. The research protocol should specify what health-care services will be made available, during and after the research, to the subjects themselves, to the community from which the subjects are drawn, or to the host country, and for how long. The details of these arrangements should be agreed by the sponsor, officials of the host country, other interested parties, and, when appropriate, the community from which subjects are to be drawn. The agreed arrangements should be specified in the consent process and document. Although sponsors are, in general, not obliged to provide health-care services beyond that which is necessary for the conduct of the research, it is morally praiseworthy to do so. Such services typically include treatment for diseases contracted in the course of the study. It might, for example, be agreed to treat cases of an infectious disease contracted during a trial of a vaccine designed to provide immunity to that disease, or to provide treatment of incidental conditions unrelated to the study. The obligation to ensure that subjects who suffer injury as a consequence of research interventions obtain medical treatment free of charge, and that compensation be provided for death or disability occurring as a consequence of such injury, is the subject of Guideline 19, on the scope and limits of such obligations. When prospective or actual subjects are found to have diseases unrelated to the research, or cannot be enrolled in a study because they do not meet the health criteria, investigators should, as appropriate, advise them to obtain, or refer them for, medical care. In general, also, in the course of a study, sponsors should disclose to the proper health authorities information of public health concern arising from the research. The obligation of the sponsor to make reasonably available for the benefit of the population or community concerned any intervention or product developed, or knowledge generated, as a result of the research is considered in Guideline 10: Research in populations and communities with limited resources.

Appendix 1

Items to be included in a protocol (or associated documents) for biomedical research involving human subjects.

(Include the items relevant to the study/project in question)

1. Title of the study;
2. A summary of the proposed research in lay/non-technical language;
3. A clear statement of the justification for the study, its significance in development and in meeting the needs of the country/population in which the research is carried out;
4. The investigators' views of the ethical issues and considerations raised by the study and, if appropriate, how it is proposed to deal with them;
5. Summary of all previous studies on the topic, including unpublished studies known to the investigators and sponsors, and information on previously published research on the topic, including the nature, extent and relevance of animal studies and other preclinical and clinical studies;
6. A statement that the principles set out in these Guidelines will be implemented;
7. An account of previous submissions of the protocol for ethical review and their outcome;
8. A brief description of the site(s) where the research is to be conducted, including information about the adequacy of facilities for the safe and appropriate conduct of the research, and relevant demographic and epidemiological information about the country or region concerned;
9. Name and address of the sponsor;
10. Names, addresses, institutional affiliations, qualifications and experience of the principal investigator and other investigators;

11. The objectives of the trial or study, its hypotheses or research questions, its assumptions, and its variables;
12. A detailed description of the design of the trial or study. In the case of controlled clinical trials the description should include, but not be limited to, whether assignment to treatment groups will be randomized (including the method of randomization), and whether the study will be blinded (single blind, double blind), or open;
13. The number of research subjects needed to achieve the study objective, and how this was statistically determined;
14. The criteria for inclusion or exclusion of potential subjects, and justification for the exclusion of any groups on the basis of age, sex, social or economic factors, or for other reasons;
15. The justification for involving as research subjects any persons with limited capacity to consent or members of vulnerable social groups, and a description of special measures to minimize risks and discomfort to such subjects;
16. The process of recruitment, e.g., advertisements, and the steps to be taken to protect privacy and confidentiality during recruitment;
17. Description and explanation of all interventions (the method of treatment administration, including route of administration, dose, dose interval and treatment period for investigational and comparator products used);
18. Plans and justification for withdrawing or withholding standard therapies in the course of the research, including any resulting risks to subjects;
19. Any other treatment that may be given or permitted, or contraindicated, during the study;
20. Clinical and laboratory tests and other tests that are to be carried out;
21. Samples of the standardized case-report forms to be used, the methods of recording therapeutic response (description and evaluation of methods and frequency of measurement), the follow-up procedures, and, if applicable, the measures proposed to determine the extent of compliance of subjects with the treatment;
22. Rules or criteria according to which subjects may be removed from the study or clinical trial, or (in a multi-centre study) a centre may be discontinued, or the study may be terminated;
23. Methods of recording and reporting adverse events or reactions, and provisions for dealing with complications;
24. The known or foreseen risks of adverse reactions, including the risks attached to each proposed intervention and to any drug, vaccine or procedure to be tested;
25. For research carrying more than minimal risk of physical injury, details of plans, including insurance coverage, to provide treatment for such injury, including the funding of treatment, and to provide compensation for research-related disability or death;
26. Provision for continuing access of subjects to the investigational treatment after the study, indicating its modalities, the individual or organization responsible for paying for it, and for how long it will continue;
27. For research on pregnant women, a plan, if appropriate, for monitoring the outcome of the pregnancy with regard to both the health of the woman and the short-term and long-term health of the child.
28. The potential benefits of the research to subjects and to others;
29. The expected benefits of the research to the population, including new knowledge that the study might generate;
30. The means proposed to obtain individual informed consent and the procedure planned to communicate information to prospective subjects, including the name and position of the person responsible for obtaining consent;
31. When a prospective subject is not capable of informed consent, satisfactory assurance that permission will be obtained from a duly authorized person, or, in the case of a child who is sufficiently mature to understand the implications of informed consent but has not reached the legal age of consent, that knowing agreement, or assent, will be obtained, as well as the permission of a parent, or a legal guardian or other duly authorized representative;
32. An account of any economic or other inducements or incentives to prospective subjects to participate, such as offers of cash payments, gifts, or free services or facilities, and of any financial obligations assumed by the subjects, such as payment for medical services;
33. Plans and procedures, and the persons responsible, for communicating to subjects information arising from the study (on harm or benefit, for example), or from other research on the same topic, that could affect subjects' willingness to continue in the study;
34. Plans to inform subjects about the results of the study;
35. The provisions for protecting the confidentiality of personal data, and respecting the privacy of subjects, including the precautions that are in place to prevent disclosure of the results of a subject's genetic tests to immediate family relatives without the consent of the subject;
36. Information about how the code, if any, for the subjects' identity is established, where it will be kept and when, how and by whom it can be broken in the event of an emergency;

37. Any foreseen further uses of personal data or biological materials;
38. A description of the plans for statistical analysis of the study, including plans for interim analyses, if any, and criteria for prematurely terminating the study as a whole if necessary;
39. Plans for monitoring the continuing safety of drugs or other interventions administered for purposes of the study or trial and, if appropriate, the appointment for this purpose of an independent data-monitoring (data and safety monitoring) committee;
40. A list of the references cited in the protocol;
41. The source and amount of funding of the research: the organization that is sponsoring the research and a detailed account of the sponsor's financial commitments to the research institution, the investigators, the research subjects, and, when relevant, the community;
42. The arrangements for dealing with financial or other conflicts of interest that might affect the judgement of investigators or other research personnel: informing the institutional conflict-of-interest committee of such conflicts of interest; the communication by that committee of the pertinent details of the information to the ethical review committee; and the transmission by that committee to the research subjects of the parts of the information that it decides should be passed on to them;
43. The time schedule for completion of the study;
44. For research that is to be carried out in a developing country or community, the contribution that the sponsor will make to capacity-building for scientific and ethical review and for biomedical research in the host country, and an assurance that the capacity-building objectives are in keeping with the values and expectations of the subjects and their communities;
45. Particularly in the case of an industrial sponsor, a contract stipulating who possesses the right to publish the results of the study, and a mandatory obligation to prepare with, and submit to, the principal investigators the draft of the text reporting the results;
46. In the case of a negative outcome, an assurance that the results will be made available, as appropriate, through publication or by reporting to the drug registration authority;
47. Circumstances in which it might be considered inappropriate to publish findings, such as when the findings of an epidemiological, sociological or genetics study may present risks to the interests of a community or population or of a racially or ethnically defined group of people; and
48. A statement that any proven evidence of falsification of data will be dealt with in accordance with the policy of the sponsor to take appropriate action against such unacceptable procedures.

Appendix 2

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI [available at:] <www.wma.net>

Appendix 3

THE PHASES OF CLINICAL TRIALS OF VACCINES AND DRUGS

Vaccine development

Phase I refers to the first introduction of a candidate vaccine into a human population for initial determination of its safety and biological effects, including immunogenicity. This phase may include studies of dose and route of administration, and usually involves fewer than 100 volunteers.

Phase II refers to the initial trials examining effectiveness in a limited number of volunteers (usually between 200 and 500); the focus of this phase is immunogenicity.

Phase III trials are intended for a more complete assessment of safety and effectiveness in the prevention of disease, involving a larger number of volunteers in a multicentre adequately controlled study.

Drug development

Phase I refers to the first introduction of a drug into humans. Normal volunteer subjects are usually studied to determine levels of drugs at which toxicity is observed. Such studies are followed by dose-ranging studies in patients for safety and, in some cases, early evidence of effectiveness.

Phase II investigation consists of controlled clinical trials designed to demonstrate effectiveness and relative safety. Normally, these are performed on a limited number of closely monitored patients.

Phase III trials are performed after a reasonable probability of effectiveness of a drug has been established and are intended to gather additional evidence of effectiveness for specific indications and more precise definition of drug-related adverse effects. This phase includes both controlled and uncontrolled studies.

Phase II and Phase III drug trials should be conducted according to Section C (Paragraphs 28–32) of the Declaration of Helsinki, which refers to medical research combined with medical care.

Phase IV trials are conducted after the national drug registration authority has approved a drug for distribution or marketing. These trials may include research designed to explore a specific pharmacological effect, to establish the incidence of adverse reactions, or to determine the effects of long-term administration of a drug. Phase IV trials may also be designed to evaluate a drug in a population not studied adequately in the pre-marketing phases (such as children or the elderly) or to establish a new clinical indication for a drug. Such research is to be distinguished from

marketing research, sales promotion studies, and routine post-marketing surveillance for adverse drug reactions in that these categories ordinarily need not be reviewed by ethical review committees (see Guideline 2).

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